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CALL FOR ABSTRACTS

The conference organizers encourage investigators to submit abstracts for poster presentations on asbestos-associated noncancer and cancer health effects and related areas. The primary objective of the conference is to improve the scientific foundation for health risk assessments of asbestos, focusing principally on nonoccupational exposures. Abstracts submitted should fall into one of the following five subject areas:

(Please see the Asbestos Health Effects Conference Web site for instructions on how to submit.)

Mineralogy and morphological characteristics of different fiber types:
Structural characteristics, surface chemistry and other physico-chemical attributes, particularly with respect to how these may (or may not) affect carcinogenicity, genotoxicity, or fibrogenesis.

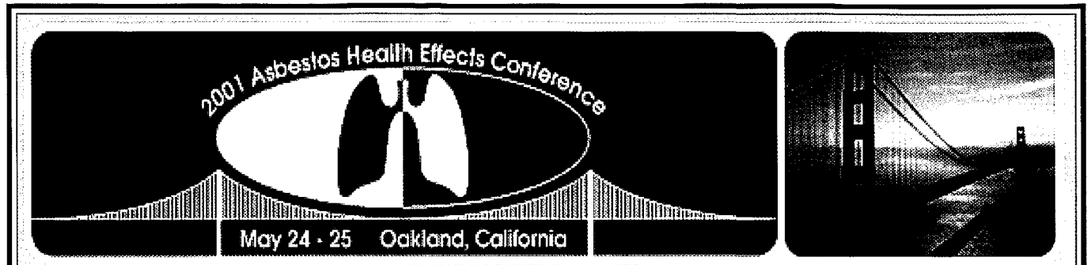
Assessment of exposure to different types of asbestos in nonoccupational settings:
Assessment of inhalation exposures or potential inhalation exposures due to the presence of different types of asbestos in soil, milling wastes, and consumer products, as well as indoor residential exposures. Of special interest would be methods for evaluating episodic exposures.

Impacts on human health:
Epidemiological studies examining the relationships of exposure to different asbestos fiber types and various health effects, including, but not limited to, mesothelioma, lung cancer, other cancers, asbestosis, and nonmalignant pleural disease.

Toxicological investigations:
Studies of toxicological mechanisms of action of asbestos. Relevant topics include cellular and molecular mechanisms underlying nonneoplastis and neoplastic response to asbestos; the influence of fiber type and exposure concentration (i.e., fiber dimensions and surface chemistry); and tissue specific (e.g., lung parenchyma, pleura, peritoneum) responses. Also, host factors which influence response to asbestos fibers.

Risk assessment methods:
Models focusing in particular on estimation of potential health risks related to exposures (including episodic exposures) to different asbestos fiber types in environmental media, consumer products, and other settings.

Abstracts must be received by April 16, 2001.



Asbestos Health Effects Conference

May 24-25, 2001
Oakland, CA

Save this Date

Join us...

for this conference to improve the scientific foundation for health risk assessments of asbestos.

Our focus will be on these topics:

- asbestos mineralogy
- exposure
- epidemiology
- mechanisms of toxicity
- carcinogenicity
- risk assessment

CA OEHHA ❖ ATSDR ❖ US EPA ❖ NIOSH ❖ MSHA

ASBESTOS HEALTH EFFECTS CONFERENCE

The primary objective of the conference is to ***improve the scientific foundation for health risk assessments of asbestos***, focusing principally on nonoccupational exposures. Included will be presentations and posters on asbestos mineralogy, exposure, epidemiology and mechanisms of toxicity and carcinogenicity. The conference will conclude with a discussion on the implications for risk assessment methods and models, focusing on the potential health risks related to nonoccupational exposures to different asbestos fiber types or fiber dimensions. The conference will include broad international participation from scientists in government, academia and the private sector, and will identify issues that need to be addressed in the next generation of risk assessments to characterize the health risks of nonoccupational exposures to asbestos.

PRELIMINARY PROGRAM

Session 1. Mineralogy & Exposure Assessment

Chair: Bruce Case, *McGill University, Canada*

John Addison, John Addison Consultancy, Scotland
"Asbestos": Which physical and mineralogical differences can or should form the basis for categorization, and how well can these categories be reproducibly separated and distinguished in the field?

Patrick Sébastien, McGill University, Canada
Measuring asbestos exposure in the field: sampling environments (air, settled dust, materials); sampling strategies; sampling instruments; and current exposures

Bruce Case, McGill University, Canada
Lung-retained fiber as a marker of retained environmental dose: Strategies, advantages, pitfalls, and coordination with epidemiological methods

Gunnar Hillerdal, Karolinska Hospital, Sweden
Radiological changes as markers of environmental exposure and environmental risk of lung cancer and mesothelioma

Session 2. Epidemiology

Chair: Julian Peto, *Institute of Cancer Research, England*

John Dement, Duke University, USA
Differences in carcinogenicity between asbestos types

Corbett McDonald, National Heart and Lung Institute, England
Carcinogenicity of fibrous tremolite in workplace and general environments

Marcel Goldberg, INSERM, France
Nonoccupational exposure to mineral fibers – what are the key determinants of exposure related to increased risks for mesothelioma and lung cancer?

Session 3. Toxicology, Pathology, Mechanisms

Chair: Kevin Driscoll, *Proctor and Gamble Pharmaceuticals, USA*

Kenneth Donaldson, Napier University, Scotland
Molecular and cellular mechanisms of asbestos fiber toxicity

Bice Fubini, University of Torino, Italy
The physical and chemical properties of asbestos fibers which contribute to biological activity

Gunter Oberdorster, University of Rochester, USA
Fiber characteristics, environmental and host factors as determinants of asbestos toxicity

Agnes Kane, Brown University, USA
Mechanisms of asbestos carcinogenesis

Session 4. Risk assessment methods

(Panel Discussion)

Chair: Gene McConnell, *Toxicology and Pathology Services Inc., USA*

The panel will examine the implications of recent scientific developments on asbestos mineralogy, exposure, epidemiology and mechanisms of toxicity and carcinogenicity for risk assessment of nonoccupational exposures to asbestos. The panel discussion will include opportunities for input from the audience. Panelists include:

Bruce Case, McGill University, Canada
Julian Peto, Institute of Cancer Research, England
Kevin Driscoll, Proctor and Gamble Pharmaceuticals, USA
Mort Lippmann, New York University, USA
Kenny Crump, ICF Kaiser Engineers, USA
Leslie Stayner, National Institute for Occupational Safety and Health, USA

INFORMATION

HOTEL INFORMATION
San Francisco Marriott
55 Fourth Street
San Francisco, CA 94103
415/896-1600

HOTEL REGISTRATION
Registrants must make their own hotel reservations with the San Francisco Marriott by Wednesday, May 2, 2001 to receive the reduced government per diem rate of $159.00 plus applicable state and local taxes (currently 14%). Please call 800/228-9290 or 415/896-1600 and ask for the EPA Asbestos Health Effects Conference.

DIRECTIONS FROM SAN FRANCISCO AIRPORT
Drive northbound on Hwy 101 into S.F. From downtown S.F., follow the sign towards the Oakland Bay Bridge. Exit in right lane at 4th St. Bear to the left with the flow of traffic onto Bryant St. Drive 1 block on Bryant St. to 3rd St. Turn left on 3rd St. and continue 4 blocks to Mission St. Turn left on Mission St. Hotel is 1 block down on right.

CONFERENCE VENUE INFORMATION
Elihu M. Harris Building
1515 Clay Street
Oakland, CA 94612
510/622-2564

BART DIRECTIONS FROM SAN FRANCISCO
Exit hotel at 4th St. entrance towards Market St. Walk one block down Market St. (toward 5th St.) to the Powell St. Station. Take the Pittsburg/Bay Point (yellow) line to the Oakland City Center/12th St. Station. The City Center/12th St. Station is two blocks east of the Elihu M. Harris Building in the City Center Retail Area. One-way fare will be approximately $2.20. Trip will be roughly 15 minutes.

PARKING
A public parking garage can be found directly across the street from the Elihu M. Harris Building at 15th and Clay Street. Hours of operation are 6:30am to 10:00pm, and costs $1.50 an hour, with a maximum of $10 per day.

ASBESTOS HEALTH EFFECTS CONFERENCE

May 24-25, 2001 at the Elihu M. Harris Building, Oakland, CA

REGISTRATION*

Register online at
www.epa.gov/swerrims/ahec/index.htm

or

Mail to
Asbestos Conference
c/o Marasco Newton Group
2425 Wilson Blvd., 4th Floor
Arlington, VA 22201

or

Fax this form to 703/526-9826 or call 703/292-5874

Please email questions to
asbestosconference@marasconewton.com

* Registration must be received by April 16, 2001.

PLEASE PRINT

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CITY _____ STATE ____ ZIP _____

TELEPHONE _____

FAX _____

E-MAIL _____

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2001 Asbestos Health Effects Conference
Oakland, California

Thursday, May 24, 2001

7:30 – 8:30 **Registration and Continental Breakfast**

8:30 – 9:15 **Welcome and Introduction, Peter Grevatt,** Environmental Protection Agency, USA
Meeting Logistics, Kim Fletcher, Marasco Newton Group, USA

9:15 – 10:05 **Session 1. Mineralogy & Exposure Assessment**

Introduction by Bruce Case, Session Chair, McGill University, Canada

John Addison, John Addison Consultancy, Scotland
"Asbestos": Which physical and mineralogical differences can or should form the basis for categorization, and how well can these categories be reproducibly separated and distinguished in the field?

10:05 – 10:20 **Break**

10:20 – 12:30 **Session 1. Mineralogy & Exposure Assessment (continued)**

Patrick Sébastien, McGill University, Canada
Measuring asbestos exposure in the field: sampling environments (air, settled dust, materials); sampling strategies; sampling instruments; and current exposures

Bruce Case, McGill University, Canada
Lung-retained fiber as a marker of retained environmental dose: Strategies, advantages, pitfalls, and coordination with epidemiological methods

Gunnar Hillerdal, Karolinska Hospital, Sweden
Radiological changes as markers of environmental exposure and environmental risk of lung cancer and mesothelioma

Discussion: Mineralogy and Exposure Assessment

12:30 – 1:30 **Lunch (on your own)**

1:30 – 3:15 **Session 2. Epidemiology**

Introduction by Julian Peto, Session Chair, Institute of Cancer Research, England

John Dement, Duke University, USA
Differences in carcinogenicity between asbestos types

Corbett McDonald, National Heart and Lung Institute, England
Carcinogenicity of fibrous tremolite in workplace and general environments

3:15 – 3:30 **Break**

3:30 – 5:00 **Session 2. Epidemiology (continued)**

Marcel Goldberg, INSERM, France

Nonoccupational exposure to mineral fibers – what are the key determinants of exposure related to increased risks for mesothelioma and lung cancer?

Discussion: Epidemiology

5:00 – 6:30 **Evening Reception and Poster Session**
(2nd Floor)

Asbestos Conference Speaker Bios

John Addison, BSc F.Min Soc.

Mr. Addison is a mineralogist with 30 years experience. His research work involves extensive studies of coal-mine dusts, asbestos minerals, toxicology of asbestos and other minerals, analysis of asbestos in autopsy cases and oil-shale studies. Mr. Addison became involved in the issues associated with asbestos in parenteral medicines.

Dr. Bruce Winston Case

Dr. Case is a pathologist and epidemiologist at McGill University in Montreal, Canada. He has practiced in pathology and epidemiology for over 30 years. In addition, Dr. Case has participated in and given lectures at workshops for many national and international agencies and professional societies on the subject of the exposure assessment and health affects of mineral fibers, including asbestos.

Kenny S. Crump, Ph.D.

Dr. Crump is Senior Vice President at The K.S. Crump Group, Inc., a consulting firm in Ruston, La.; is an Adjunct Professor of Chemical Engineering at Louisiana Tech University; and is an Adjunct Professor of Toxicology for the College of Pharmacy and Health Sciences at Northeast Louisiana University. He has testified on numerous occasions about the health effects of asbestos.

John M. Dement, Ph.D.

Dr. Dement is an Associate Professor for the Division of Occupational & Environmental Medicine in the Department of Community & Family Medicine at Duke University Medical Center. He has served the National Institute for Occupational Safety and Health as the Director of the Office of Disease Prevention and Exposure Research and as the Deputy Director for the Division of Respiratory Disease Studies.

Kevin E. Driscoll, Ph.D.

Dr. Driscoll received his Ph.D. in Environmental Health Science, Inhalation Toxicology from New York University in 1986. He currently serves as the Associate Director for Cell & Molecular Core and Cardiovascular Research at Procter & Gamble Pharmaceuticals. Dr. Driscoll has spent 20 years studying respiratory toxicology.

Dr. Bice Fubini

Dr. Fubini was educated at the University of Torino (Italy); and is currently the Head of the Interdepartmental Center "G.Scansetti" for Studies on Asbestos and other Toxic Particulates, and an Associate Professor of General and Inorganic Chemistry in the Chemistry Department. In the past twenty years, Dr. Fubini has developed studies on the chemical basis of the toxicity of solid materials.

Dr. Marcel Goldberg

Dr. Goldberg graduated from Pierre et Marie Curie University, Pitié-Salpétrière Medical School, in Paris in 1972. Dr. Goldberg currently serves as a Professor of Epidemiology at René Descartes University, Paris-Ouest Medical School; and is the Head of the "Health and Work" Department of the French National Institute for Health Surveillance (InVS).

Dr. Gunnar Hillerdal

Dr. Hillerdal is a specialist in respiratory medicine with over 28 years of experience. He currently serves as the Senior Physician at the Lung Hospital in Karolinska Hospital. In addition, Dr. Hillerdal has written numerous papers about the health effects of asbestos on the lungs.

Agnes B. Kane, Ph.D.

Dr. Kane is the Chair for Brown University's Department of Pathology & Laboratory Medicine. She has over 25 years of experience studying human pathology. Dr. Kane is a reviewer for numerous revered science and pathology journals. In addition, she was one of the original organizers for the workshop on *Approaches to Evaluating Toxicity and Carcinogenicity of Man-made Fibers.*

Morton Lippmann, Ph.D.

Dr. Lippman, a Professor at New York University (NYU) Medical Center, also serves as: the Director of the EPA/NYU Particulate Matter Health Effects Research Center; Director of the Human Exposure and Health Effects Program at the Nelson Institute of Environmental Medicine at NYU Medical Center; and Director of the Aerosol and Inhalation Research Laboratory at NYU Medical Center.

Ernest E. McConnell, DVM, MS (Path)

Dr. McConnell has spent over 30 years studying veterinary pathology. He currently serves as the President of ToxPath Inc., in Raleigh N.C. Dr. McConnell is an expert in inhalation toxicology and has published over 122 papers concerning animal toxicology.

Dr. John Corbett McDonald

Dr. McDonald has over 60 years experience as an epidemiological researcher. He currently serves as Professor Emeritus at London University's Department of Occupational and Environmental Medicine. He has written many epidemiological research papers, especially covering occupational health.

Günter Oberdörster, Ph.D.

Dr. Oberdörster is a Professor of Toxicology in Environmental Medicine at the University of Rochester in Rochester, NY. For the University of Rochester, he also serves as Head of the Division of Respiratory Biology & Toxicology at the School of Medicine, and a Professor of Oncology at School of Medicine and Dentistry. In addition, Dr. Oberdörster is the Director of UR-EPA Particulate Matter Center.

Julian Peto, Ph.D.

Dr. Peto is a Cancer Research Campaign Professor of Epidemiology, and Head of the Section of Epidemiology at the Institute of Cancer Research in Surrey, England. Since 1998, the CRC Chair of Epidemiology has been held jointly with the London School of Hygiene and Tropical Medicine. He has over 18 years specializing in cancer research.

Leslie Thomas Stayner, Ph.D.

Dr. Stayner received a Ph.D. in Epidemiology from the University of North Carolina in 1989. Dr. Stayner currently serves as the Chief of the Risk Evaluation Branch for the National Institute for Occupational Safety and Health, Education and Information Division in Cincinnati.

Cynthia R. Timblin, Ph.D.

Dr. Timblin currently serves as Research Assistant Professor at the University of Vermont in Burlington, VT. In addition, she was a postdoctoral fellow at the Fred Hutchinson Cancer Research Center in Seattle, WA, and for the NIEHS Environmental Pathology Training Grant at the University of Vermont. Dr. Timblin has published many papers on gene research. She received her Ph.D. in Biological Sciences from the University of Maryland, Baltimore Co., Catonsville, MD.

Asbestos Health Effects Conference
An Overview of Key Issues

Peter C. Grevatt, Ph.D.
U.S. EPA, Washington, DC

Asbestos Health Effects Conference
Oakland, California
May 24-25, 2001

Purpose of Conference

- Sound science in asbestos risk assessment
  - Revisit key questions on asbestos health effects
  - Identify areas of general agreement
  - Update risk assessment methods

Current US Risk Assessment Approaches for Asbestos

-15yr. old Health Assessment document (1986).

- Treat all forms of asbestos equally
- Fiber enumeration based on PCM analysis
  - Count only fibers > 5 microns
  - Fibers > 5 microns are equipotent
- Noncancer endpoints not addressed

-IRIS acknowledge possible differences in fiber type + dimension - insuff. data to distinguish at that time.

Fiber Type

- Amphibole hypothesis: Chrysotile less potent than amphiboles for asbestosis and cancer
  - Can the carcinogenic risks from chrysotile and amphibole exposures be distinguished?
  - Can the asbestosis risks from chrysotile and amphibole exposures be distinguished?

Fiber Dimensions

- Which fiber dimensions are important to enumerate?
  - Can the carcinogenic risks from long and short fibers be distinguished?
  - Can the asbestosis risks from long and short fibers be distinguished?
- What techniques are best for measurement and enumeration of asbestos fibers?
  - How should PCM and TEM counts be converted?

Mechanisms of Toxicity

- Molecular and cellular mechanisms of toxicity
  - Critical physical and chemical properties
  - Environmental and host factors

Risk Assessment

- Fiber type
- Fiber size
- Exposure assessment
  - Risks from episodic exposures
- Assessment of asbestosis, other cancers
- Assessment of mixtures
- "Transitional" and "cleavage fragments"

Mineralogy and Exposure Assessment

Introduction: Bruce Case

Dedicated to the memory of Chris Wagner

DIFFUSE PLEURAL MESOTHELIOMA AND ASBESTOS EXPOSURE IN THE NORTH WESTERN CAPE PROVINCE

BY

J. C. WAGNER, C. A. SLEGGS, and PAUL MARCHAND

From the Pathology Division, Pneumoconiosis Research Unit of the Council for Scientific and Industrial Research, Johannesburg, West End Hospital, Kimberley, and the Department of Thoracic Surgery, University of the Witwatersrand and Johannesburg General Hospital

(RECEIVED FOR PUBLICATION APRIL 24, 1960)

From the addendum: by June 1960 there were 47 mesotheliomas; 45 associated with crocidolite exposure

"In failing to take more seriously the paper published by Wagner et al. in 1960 the world made a costly mistake"

- McDonald JC 1995

What is now generally accepted

- regarding asbestos mineralogy ?
- regarding exposure assessment for "asbestos"?
- We need to step back from these to more general questions first

What *is* "asbestos"?

- John Addison will tell us!

But...

- IARC 1996: " "Asbestos" is often inappropriately used as a generic, homogeneous rubric, and even when an asbestos fibre type is specified, its source is rarely stated."

Defining "asbestos" (continued)

- Wagner, ILO/ NIOSH, 1990:

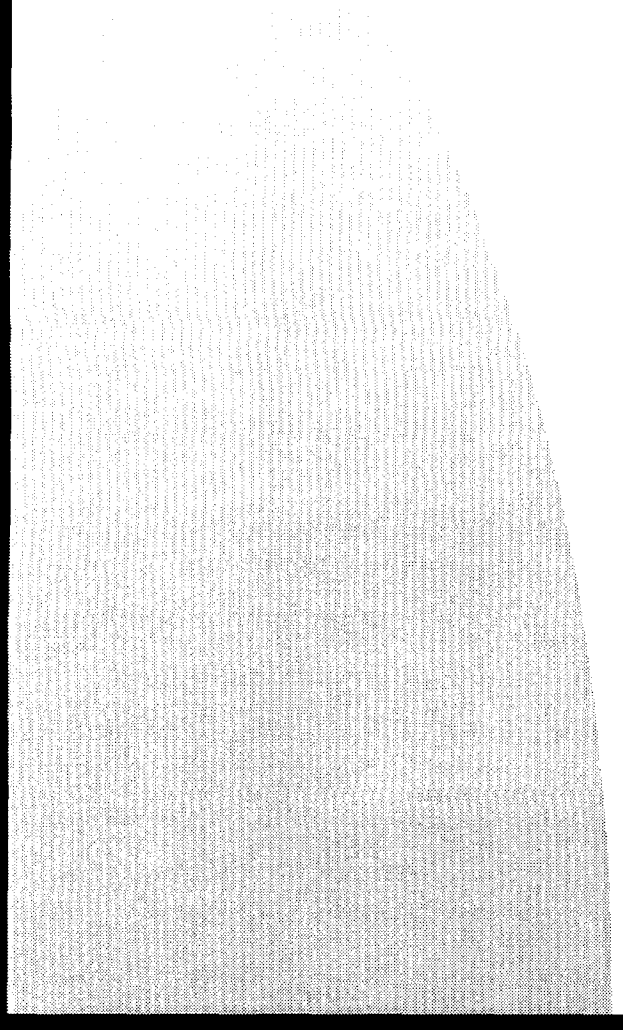
- asbestos may be defined as "a group of fibrous minerals that can be split longitudinally and have commercial uses".

- Wagner also noted that "the term asbestos was originally used for chrysotile:

Defining "asbestos" (continued)

- ..."If this had been maintained and the other minerals referred to as the amphibole fibres, the present confusion in assessing the risk hazard would not have occurred"

- Wagner JC. (1990) (NIOSH) Publication No. 90-108, Part I, pages 22-24.



BUT...

Geolib® Standard Report

Mineral Class: VIIIca Silicates

(Inosilicates – Amphibole)

Number of Minerals: 38

ACTINOLITE ANTHOPHYLLITE ARFVEDSONITE BARROISITE CROSSITE CUMMINGTONITE ECKERMANNITE EDENITE FERRIKATOPHORITE-(?) FERRIWINCHITE FLUOR-FERRO-LEAKEITE GEDRITE GRUNERITE HASTINGSITE KATOPHORITE KORNITE LEAKEITE MAGNESIO-ANTHOPHYLLITE MAGNESIO-ARFVEDSONITE MAGNESIOCLINOHOLMQUISTITE MAGNESIOCUMMINGTONITE MAGNESIOFERRIKATOPHORITE MAGNESIOGEDRITE MAGNESIOKATOPHORITE MAGNESIORIEBECKITE MANGANO-GRUNERITE MANGANOCUMMINGTONITE NYBOITE-(?) PARGASITE POTASSIUM-FLUOR-RICHTERITE RICHTERITE RIEBECKITE SODIUMANTHOPHYLLITE SODIUMGEDRITE TREMOLITE TSCHERMAKITE UNGARETTIITE

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Thus the questions must be asked:

1. Which physical or mineralogical differences *CAN OR SHOULD* form the basis for categorization?
2. Can these categories be reproducibly distinguished (AND separated)?
3. "asbestiform" ?, "cleavage fragments" ?? "transitional fibers" ???
4. Which types and dimensions of fibers are important to enumerate? (implies EM, so...)

Ideally risk assessors could agree upon well-defined parameters of concern:

Which **mineral categories (e.g. fiber types)**

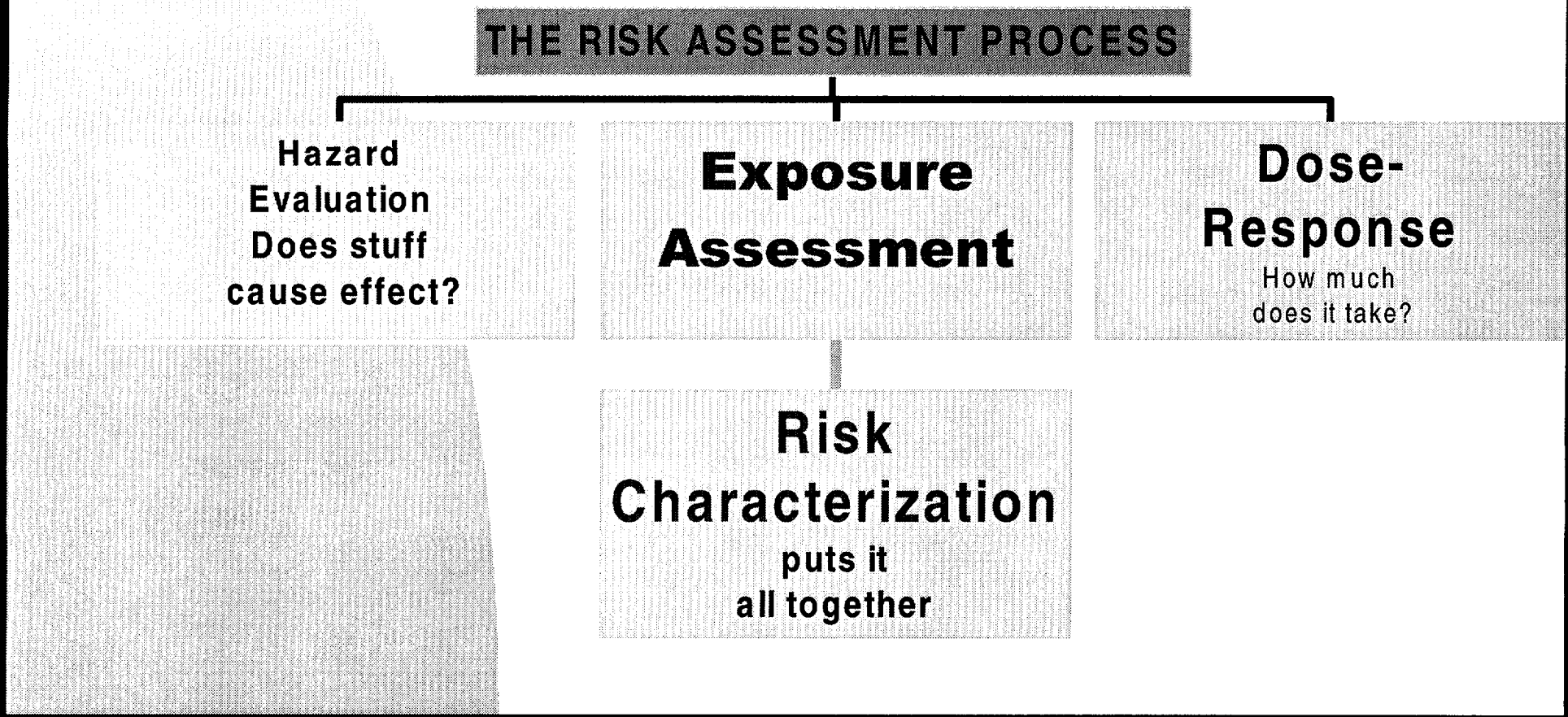
cause which disease(s) (or not!!)

at *which*

- **Exposure (-→ dose)**
- **Length (range?) Width (range?)**
- **Chemistry, crystallography…**

So much for mineralogy; where does "exposure assessment" fit in?

Exposure assessment is a part of risk assessment



The first part of "exposure assessment" is *measurement*

1. WHAT do we measure?
2. WHERE do we measure? (air? "settled dust"? Materials which may *contain* the asbestos? Lung tissue?)
3. HOW do we measure? (instruments? Procedures? e.g. NIOSH 7400/7402)?

The first part of "exposure assessment" is *measurement (continued)*

4. How do we DEFINE and EXPRESS THE RESULTS?

Example: Detection limits:

Too sensitive – "positive" in this room – so what?

Too insensitive – can miss exposures of interest.

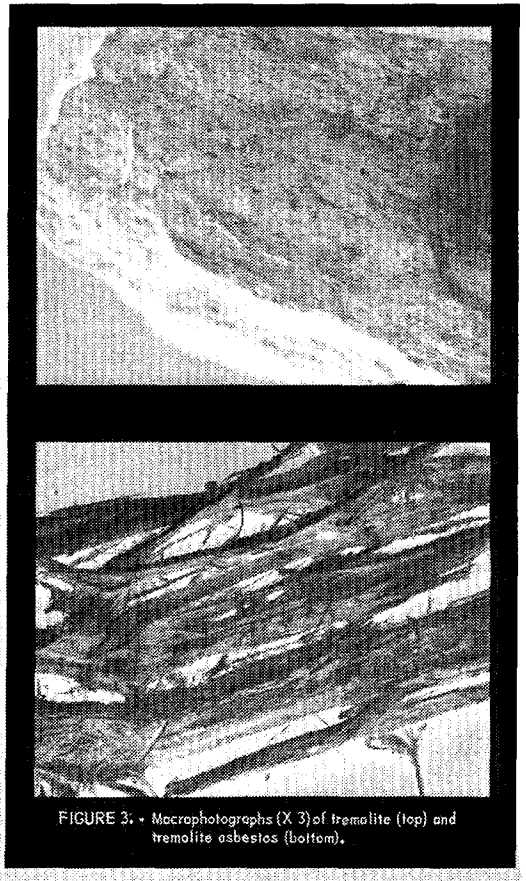
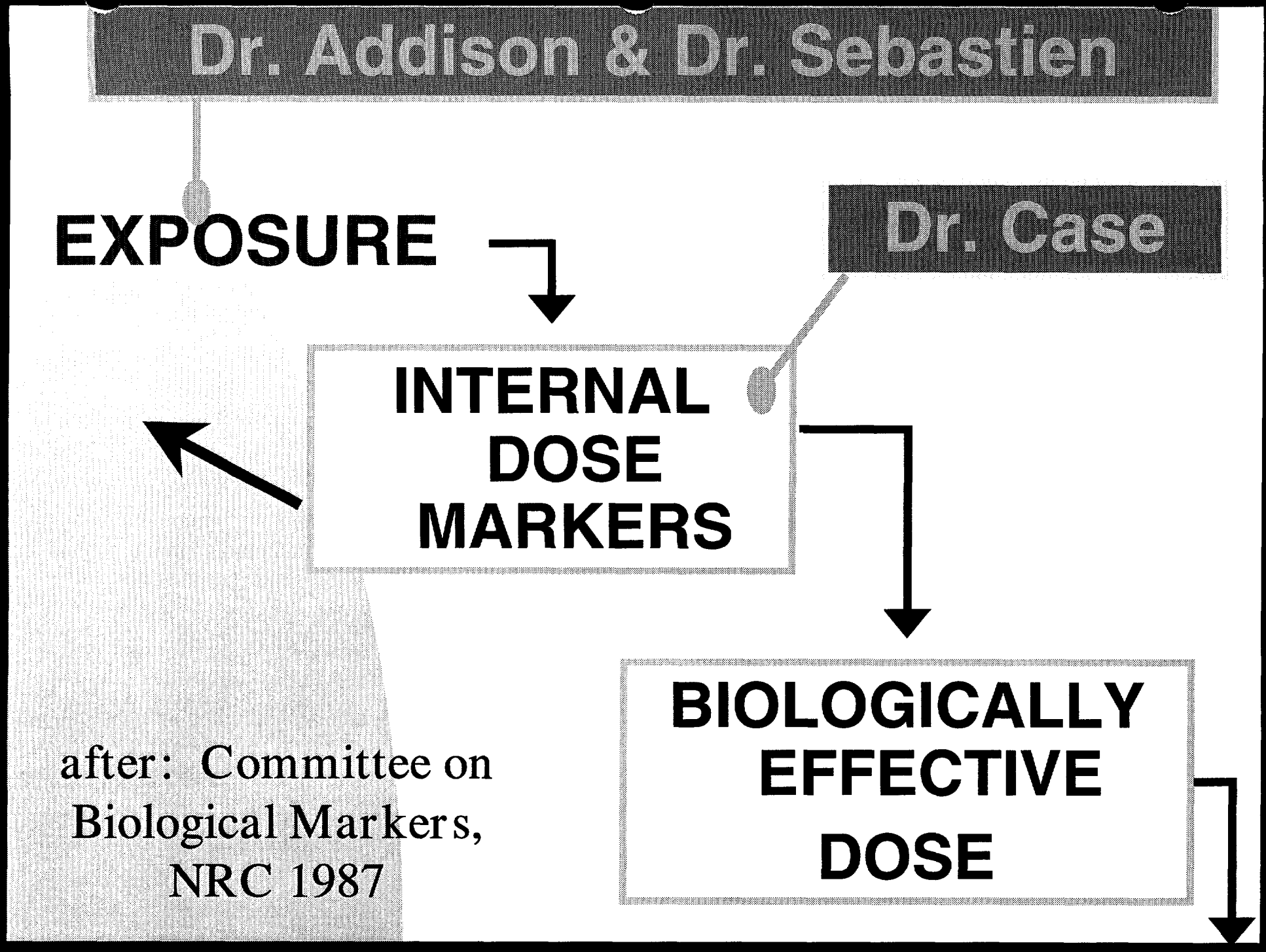


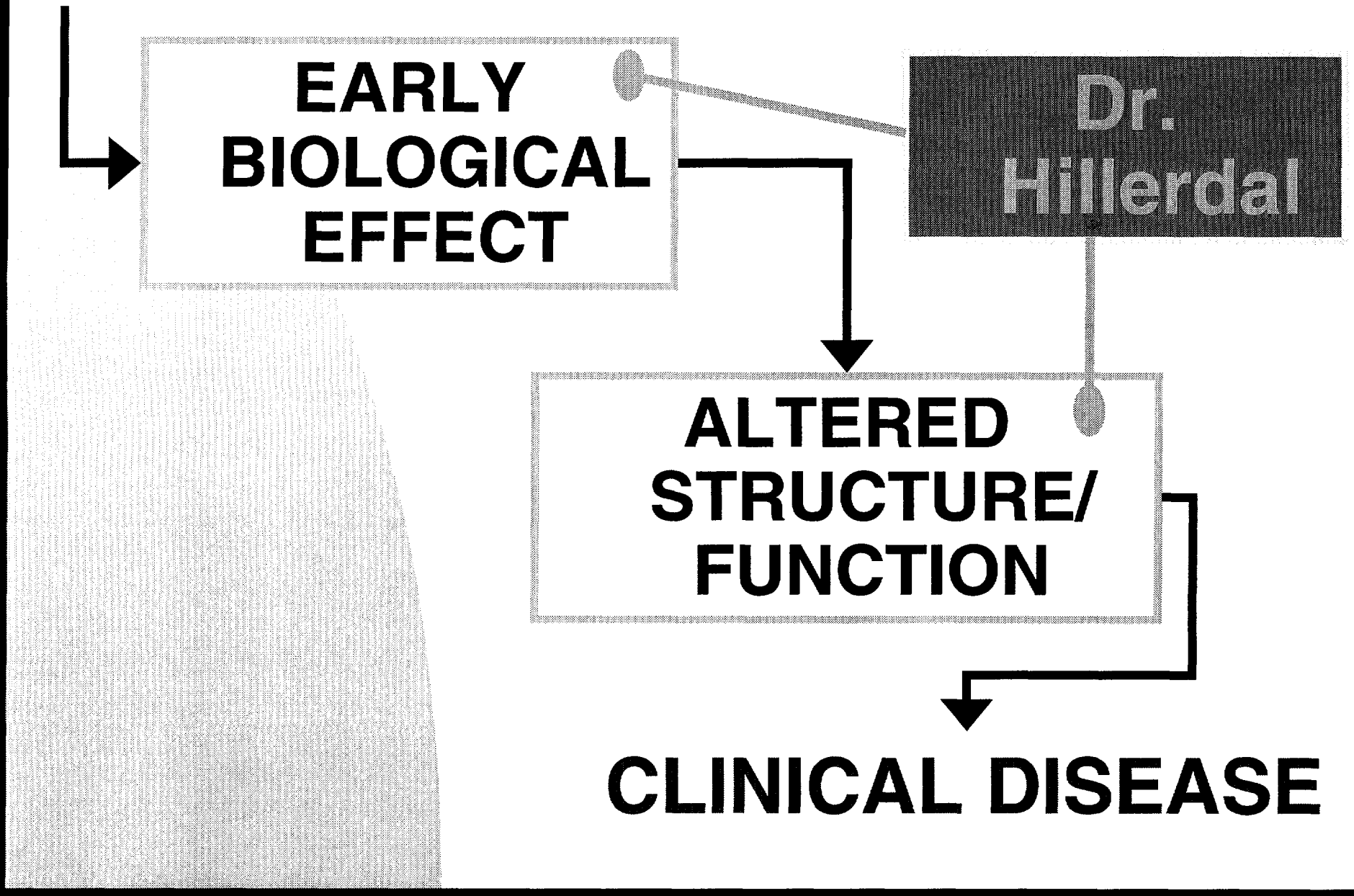
FIGURE 3. • Macrophotographs (X 3) of tremolite (top) and tremolite asbestos (bottom).

From exposure to dose

1. **What is in the ground?**
2. **What is, or *can be*, *on* the ground and *in the air*?**
3. **What is, or *can be*, in the lung (and how and why does it get there, and what happens to it there, and**
4. ***what happens to US*, after that)**


Dr. Addison & Dr. Sebastien
EXPOSURE
Dr. Case
INTERNAL DOSE MARKERS
BIOLOGICALLY EFFECTIVE DOSE
after: Committee on Biological Markers, NRC 1987

Putting exposure in perspective: 2



The Mineralogy of Asbestos

John Addison

John Addison Consultancy

Introduction

- To clarify the definitions of some mineralogical terms
- To assess the mineralogy of the serpentine and amphibole minerals
- To identify those mineral properties that distinguish the asbestos forms

Terms for clarification

- Asbestiform
- Cleavage fragment
- Transitional fibres
- Asbestos

ASBESTIFORM

- ASTM definition for a mineral habit
- Applies to many different non-asbestos minerals
- Does not imply all of the physical, chemical or toxicological properties of asbestos
- It only means "resembling asbestos"

Asbestiform fibres

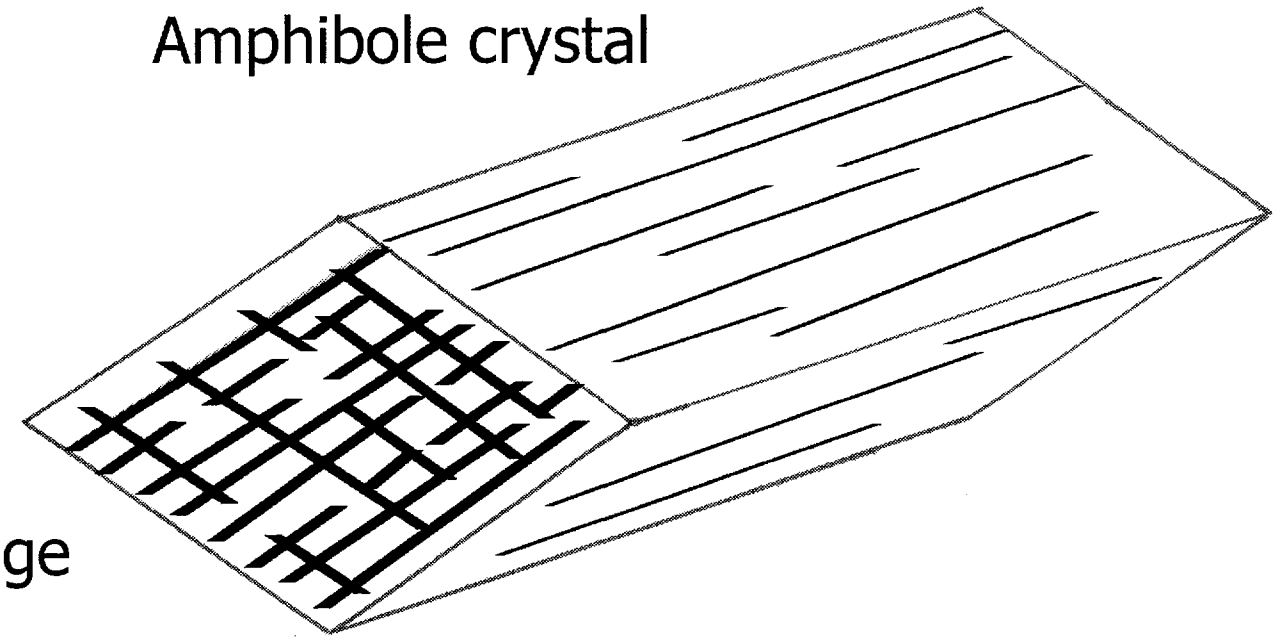
- Asbestiform Fibres are not 'longer than 5 microns with an aspect ratio of 3:1'
- Shape characteristics devised for counting fibres in microscopy should not be used to define the identity of mineral fibres.

Cleavage

- Most minerals have a tendency to break along systematic sets of planes of weakness in their crystal lattice. These are called cleavages
- Some minerals have one perfect cleavage e.g. Muscovite mica. These split easily into thin transparent flakes.
- Other minerals have two or more sets of cleavage planes.
- All amphiboles have two cleavages at 56^{o} to each other, parallel to the long axis of the crystal.

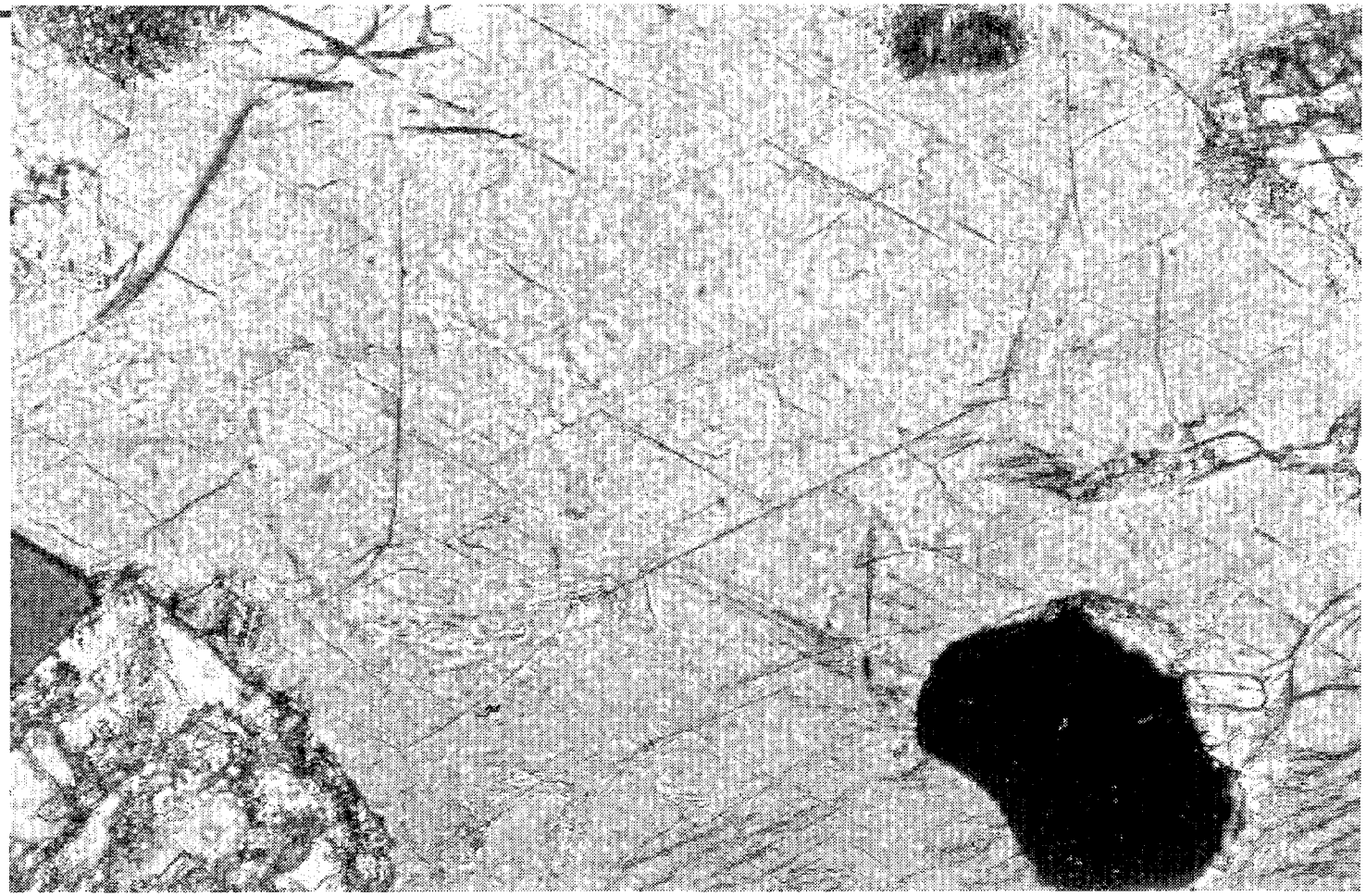
Cleavage

Amphibole crystal



Cleavage planes

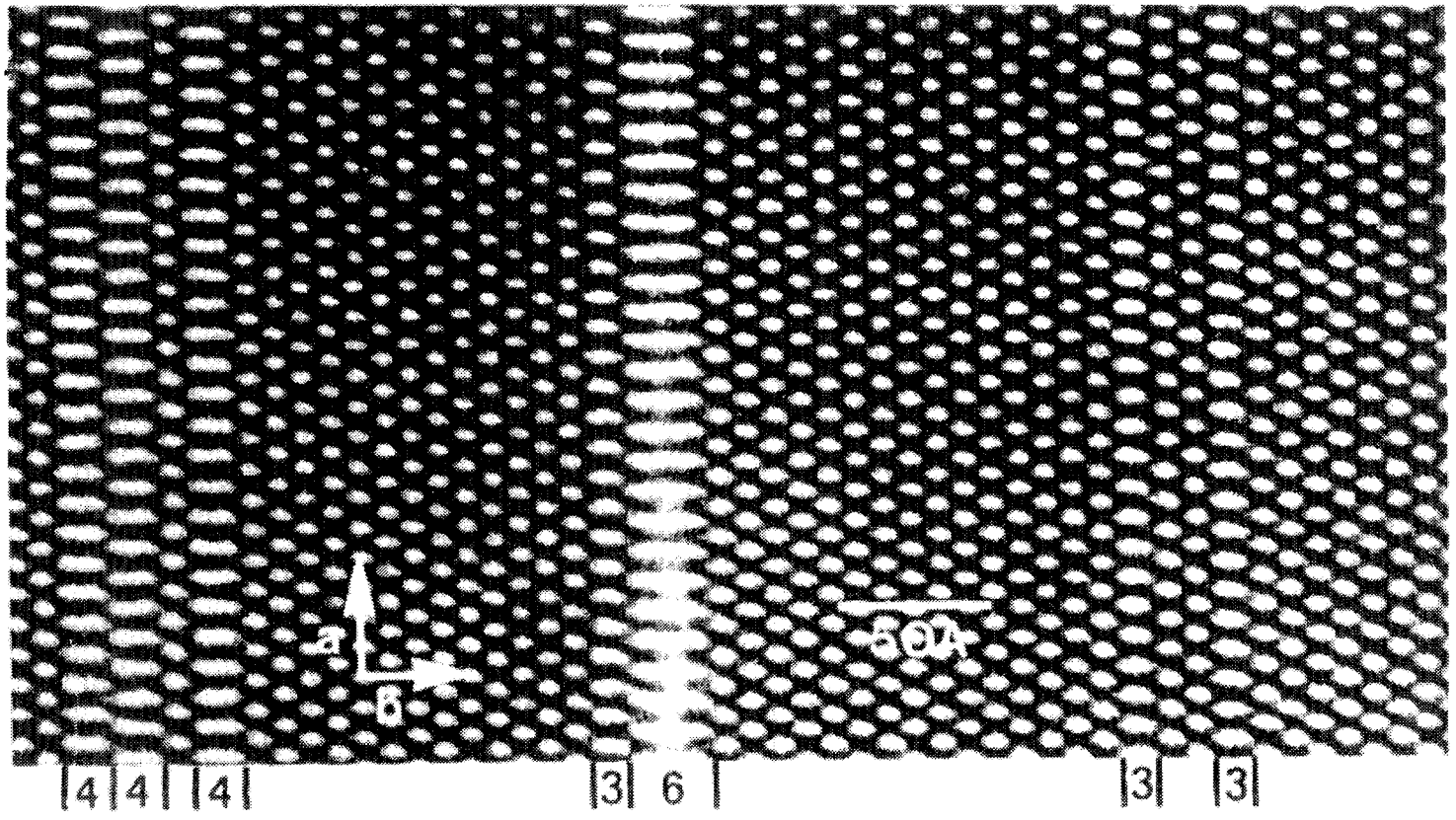
Cleavage traces in thin section of amphibole



TRANSITIONAL FIBRES

- Transitional fibres are sub-microscopic intergrowths of two or more minerals.
- They may be primary crystal growth
- They may also be the result of retrograde metamorphic conversion of an earlier mineral into two phases.
- Crystal lattice orientations of the two minerals are often similar.

Transitional fibres. Anthophyllite



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Veblen 1991

Asbestos Definitions 1

- Most of the definitions of asbestos in the legislation of Europe and the USA are inadequate.
- Many amphibole asbestos types are not included. Richterite, winchite etc.
- Fibre shape criteria are mistakenly taken as part of the definition.

Asbestos definitions 2

- The use of terms such as 'fibrous' tremolite is ambiguous.
- The definition of 'asbestos containing material' is inappropriate (1% in USA, or 'any' asbestos in UK) – 1% is too high; zero is impossible to prove.

ASBESTOS : Chrysotile

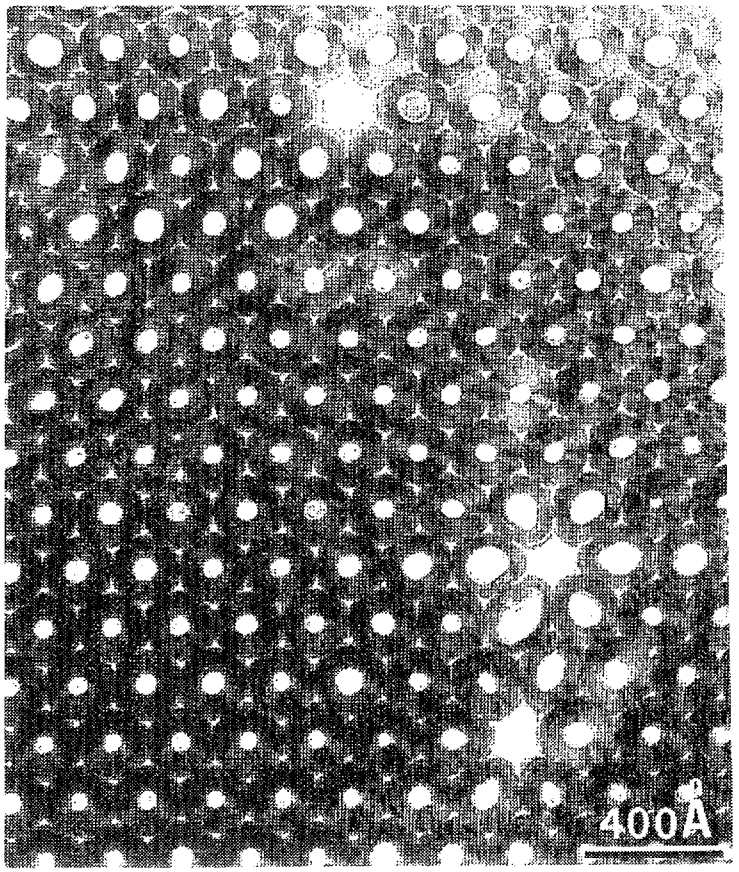
- One of the serpentine group of minerals
- 'Unique' tubular crystal structure
- Environmentally ubiquitous
- Several polymorphs, but all are still chrysotile asbestos
- Antigorite, Lizardite serpentine are not polymorphs of chrysotile

Chrysotile

- Chemically less stable than amphiboles
- Lower persistence in lung tissue
- Some is described as 'short fibre' chrysotile. Lower toxicity?

Chrysotile

- HRTEM image of chrysotile fibrils
- Cylindrical crystals 25-30 nm diameter
- (Baronnet 1992)



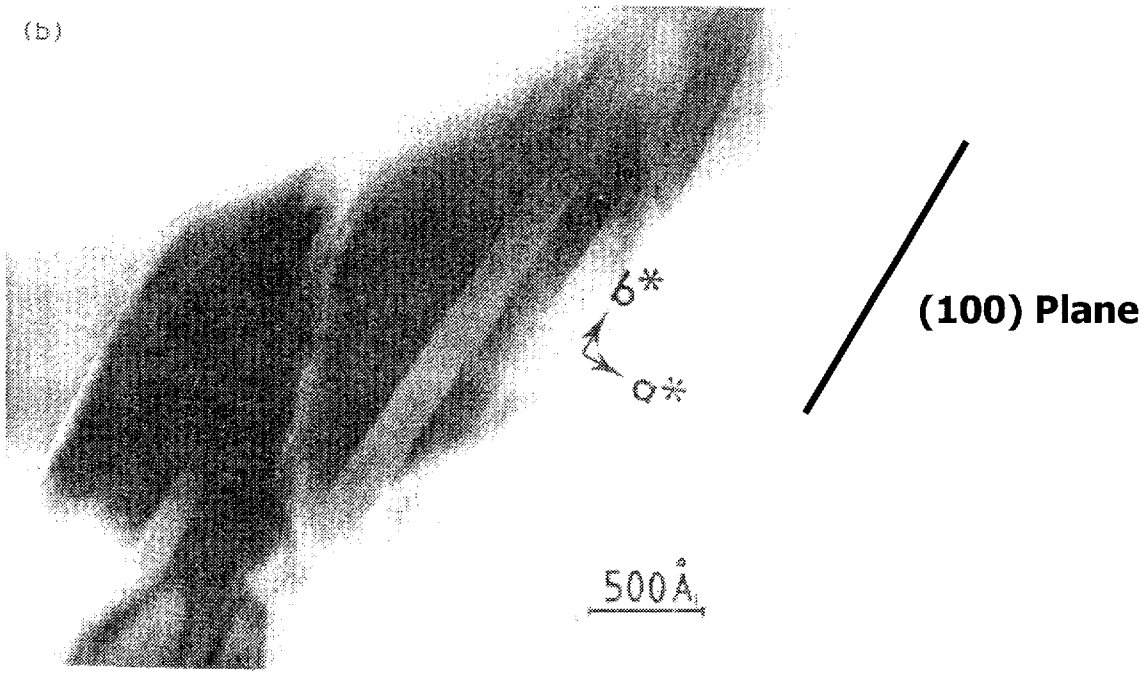
Asbestos: Amphiboles

- The tendency of asbestos amphiboles to occur as long thin fibres appears to be related to the presence of two other crystallographic properties in addition to the cleavages
- These are:
- Multiple twinning
- Chain width disorder planes

Multiple Twinning

- Twinning of crystals refers to a systematic re-orientation of the crystal lattice across a plane. It often produces a mirror image reversal of the symmetry of the structure.
- Multiple twinning describes repeated fine scale reversals of the structure.
- The amphiboles usually twin across planes parallel to the long axis of the crystal, and perpendicular to the a axis of the crystal [i.e. (100)].
- These planes are also partings or cleavages

Multiple twinning in actinolite asbestos

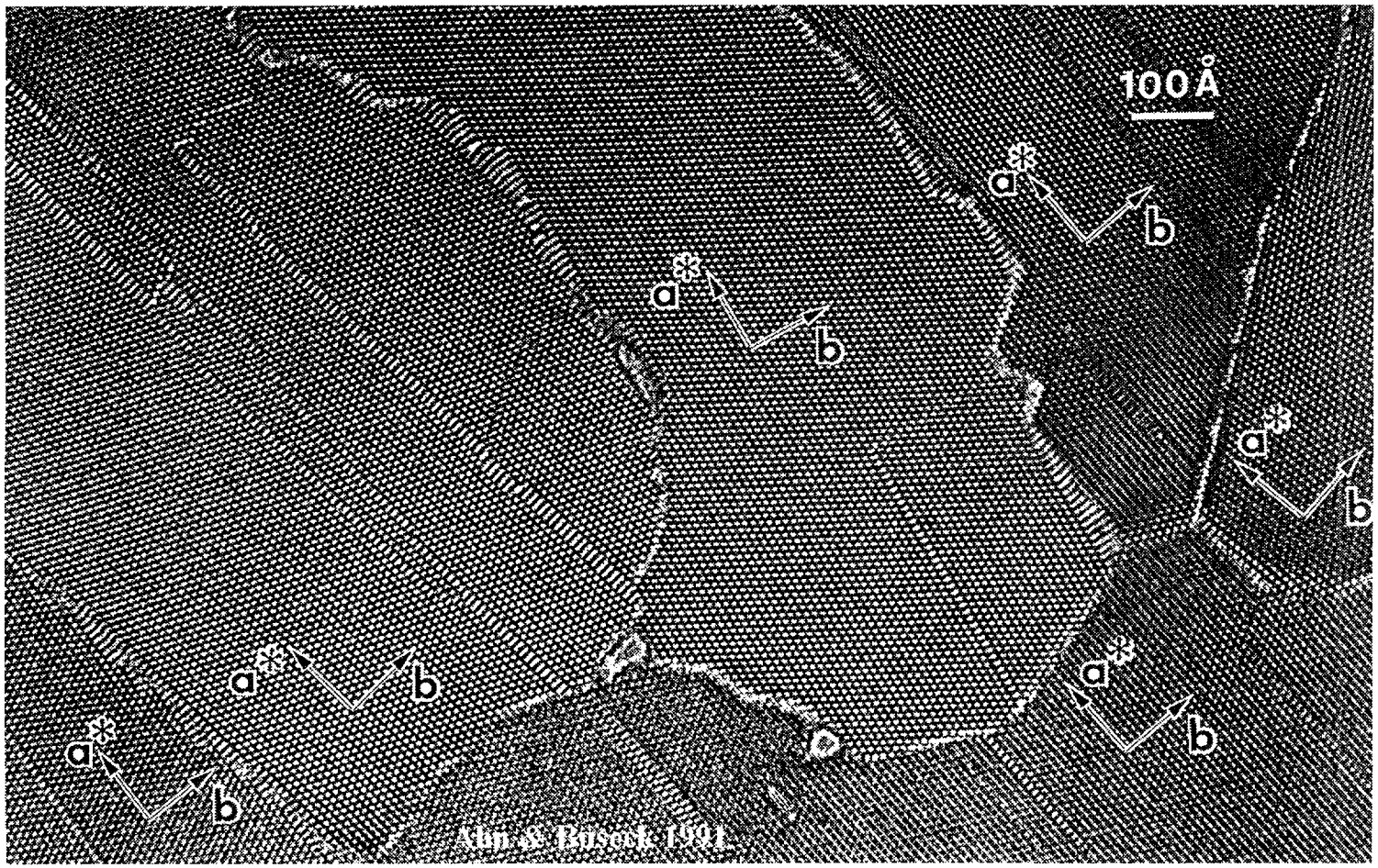


Dorling & Zussman 1987

Amphibole chain structures

- All amphiboles have a double chain silicate structure.
- Triple or higher multiple chains can occur along planes within the structure
- These planes are parallel to the long axis of the crystal, and perpendicular to the b axis [i.e. on (010)]
- Multiple chain disorders are more common in amphibole asbestos

Chain width disorder: Crocidolite



Twinning and Multiple chains

- When both multiple twinning and chain width disorders occur at high frequency there is a much greater tendency to form long thin fibres
- The two partings, at right angles to each other and parallel to the long axis of the crystal form the long thin lath shaped fibres often seen in amphibole asbestos
- The partings also tend to terminate incipient transverse cracks, so enhancing the tensile strength of the fibres

Si vs Na + K in Calciferous Amphiboles

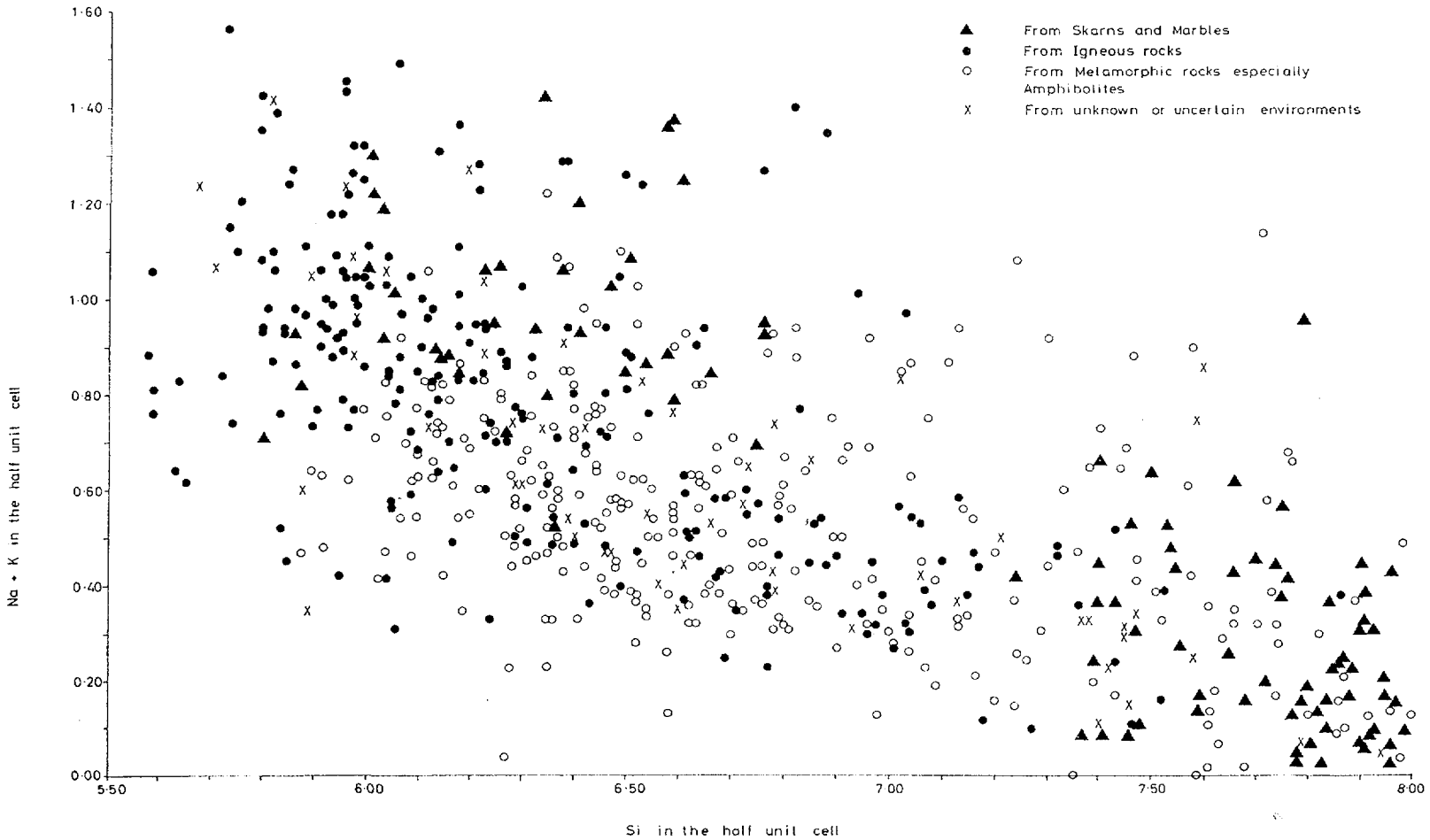
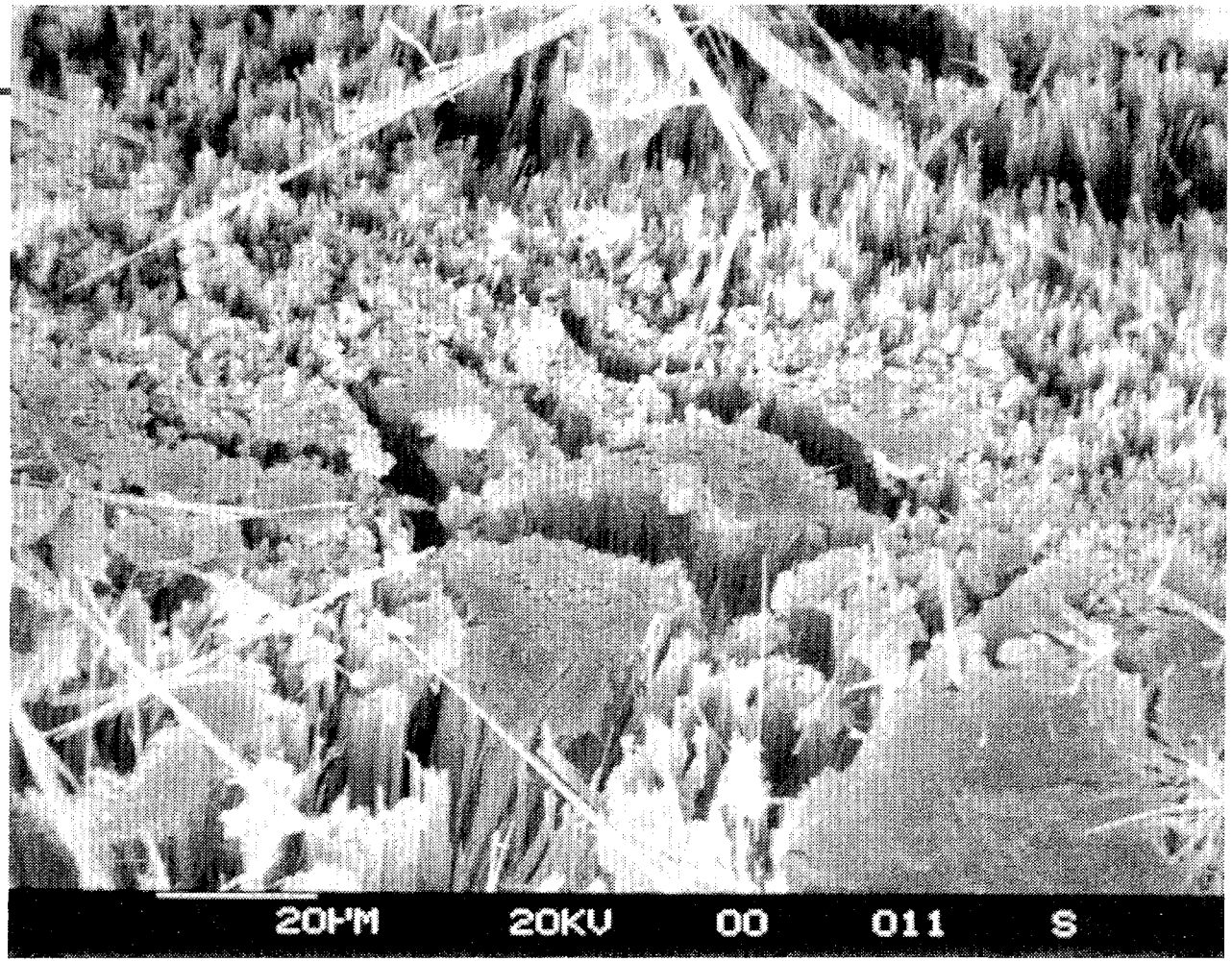


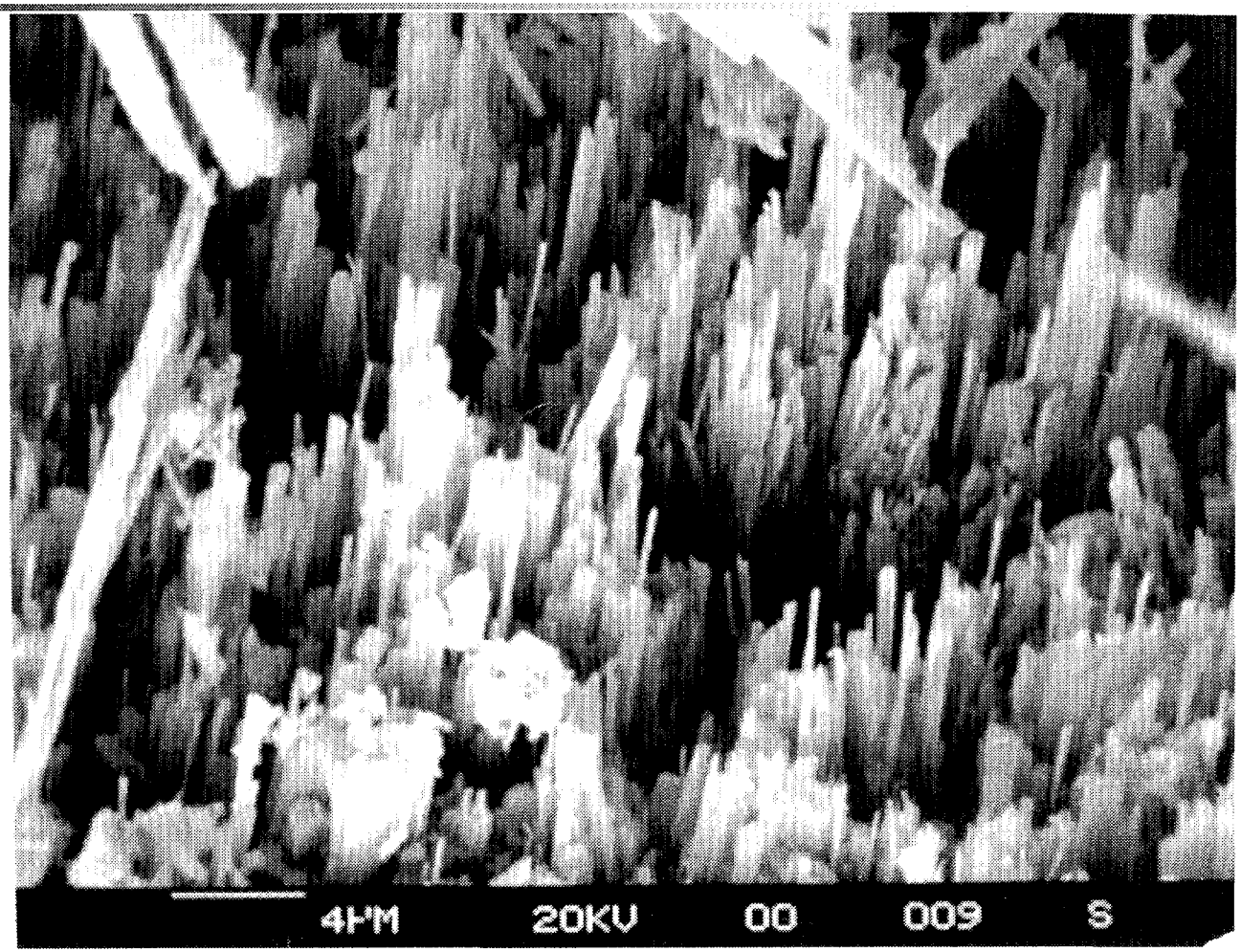
Figure 11. Plot of Na+K against Si in the half-unit cell for the first 936 amphiboles analyses in Table 2.

Leake 1968

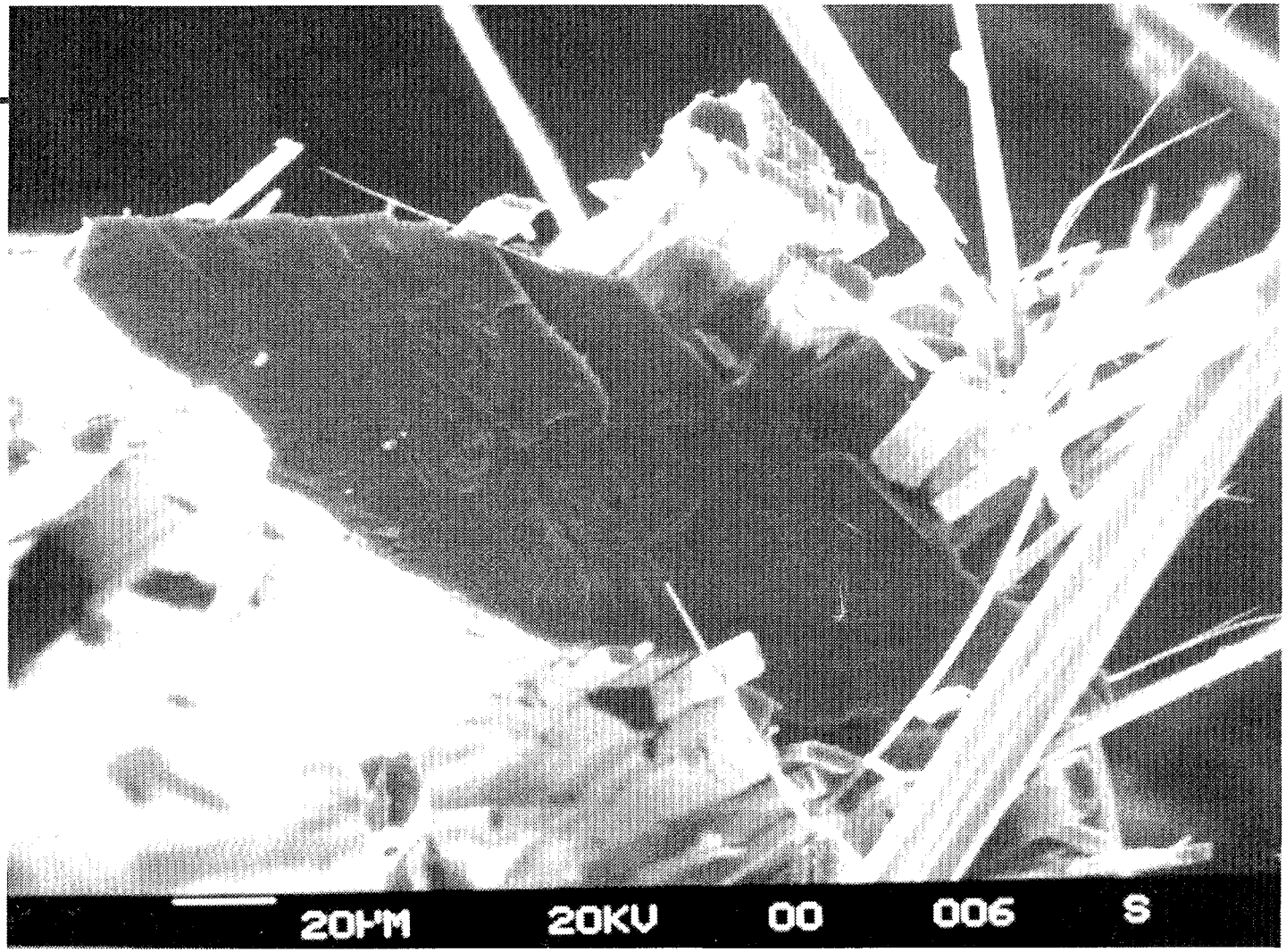
Tremolite Asbestos from Jamestown, California



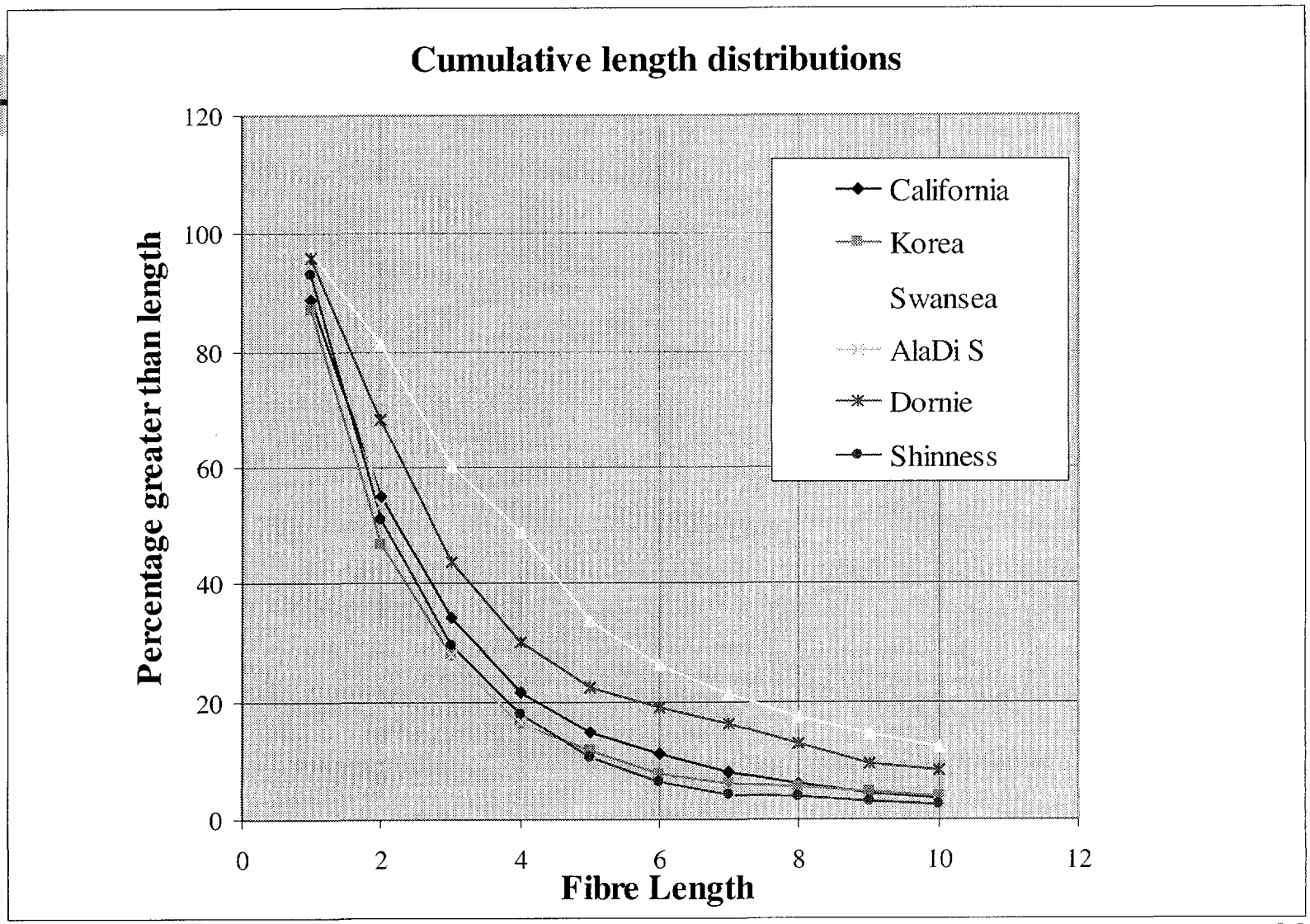
Tremolite; Jamestown



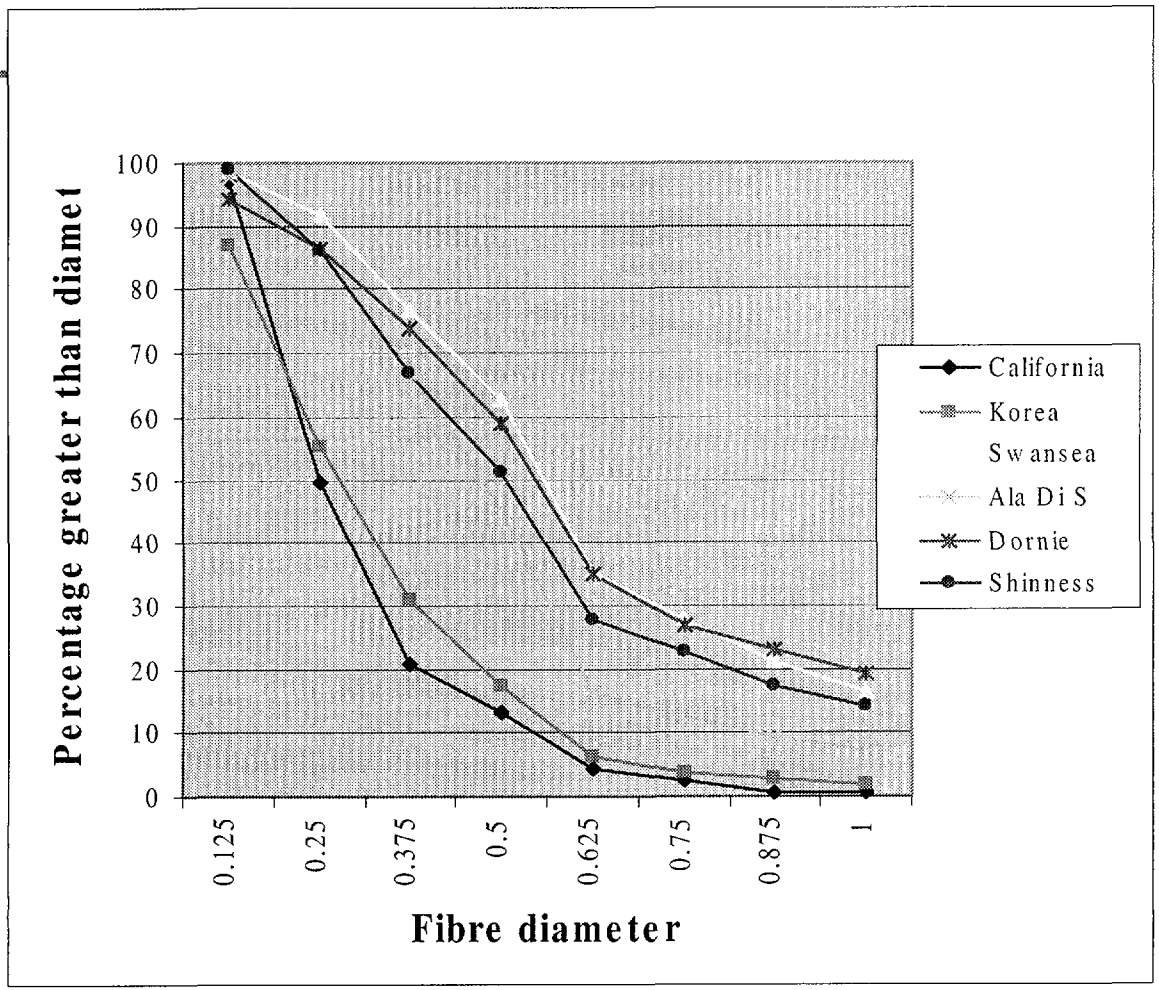
Tremolite fibres from Ala di Stura



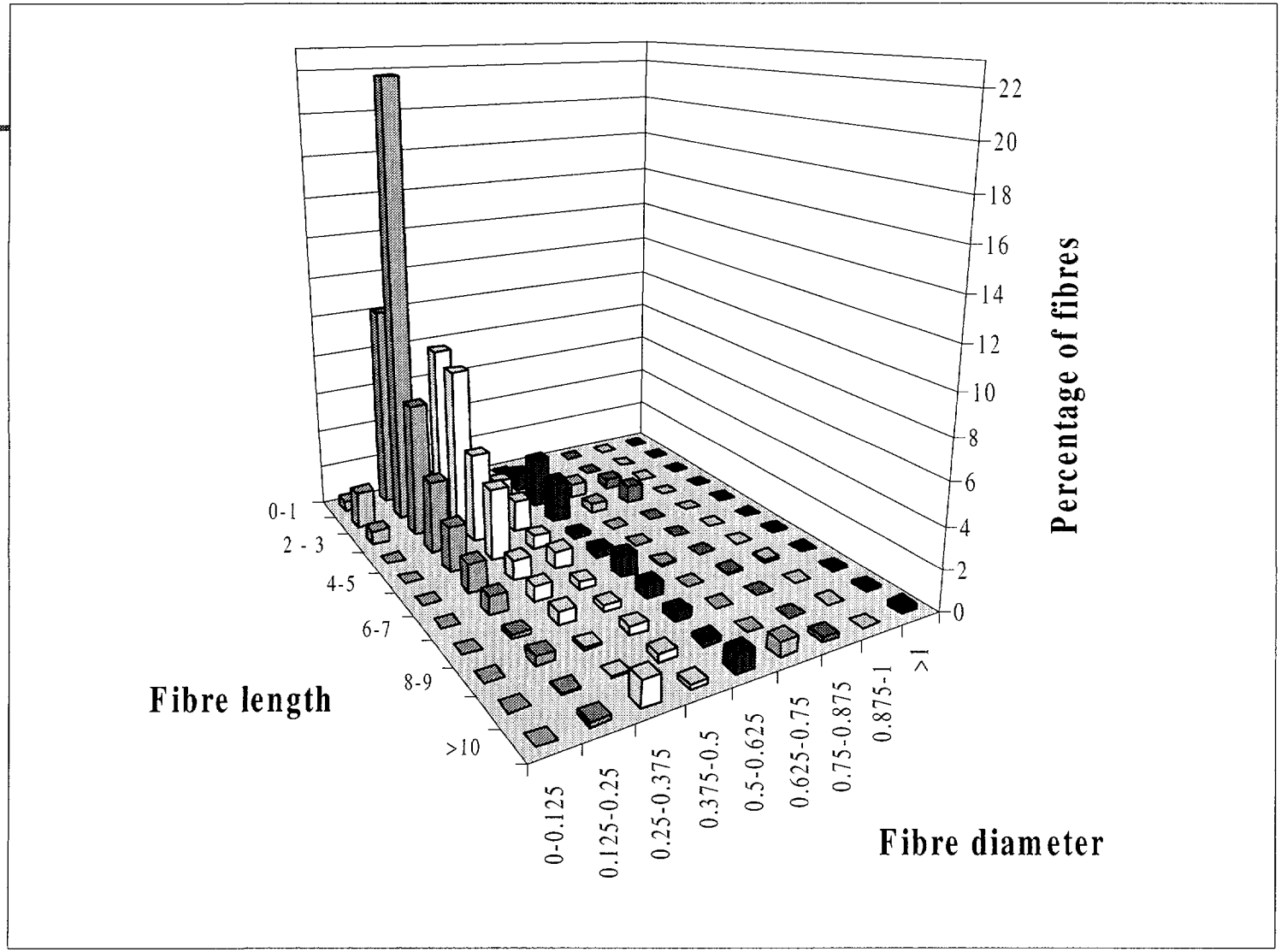
Tremolite length distributions



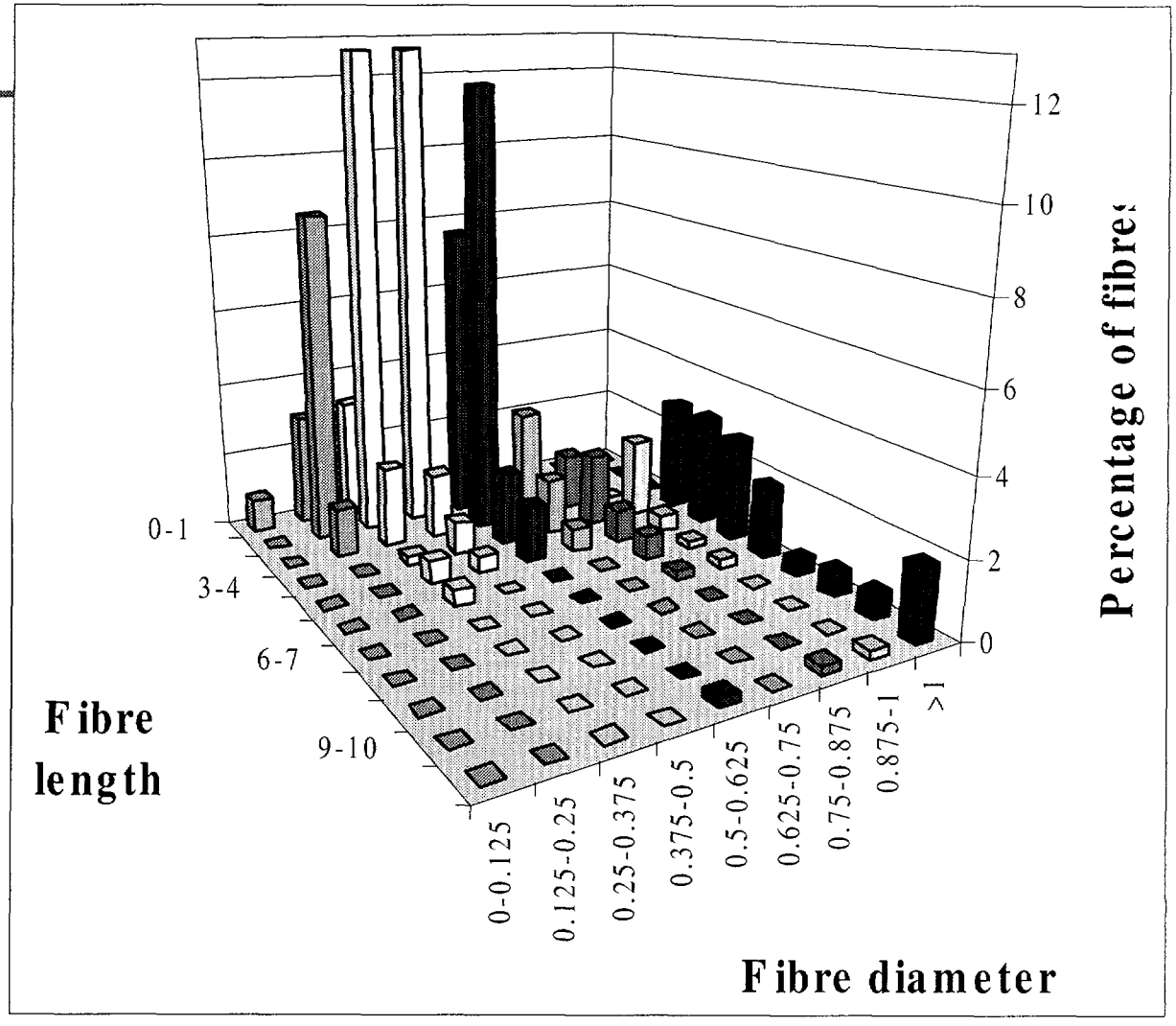
Tremolite diameter distributions



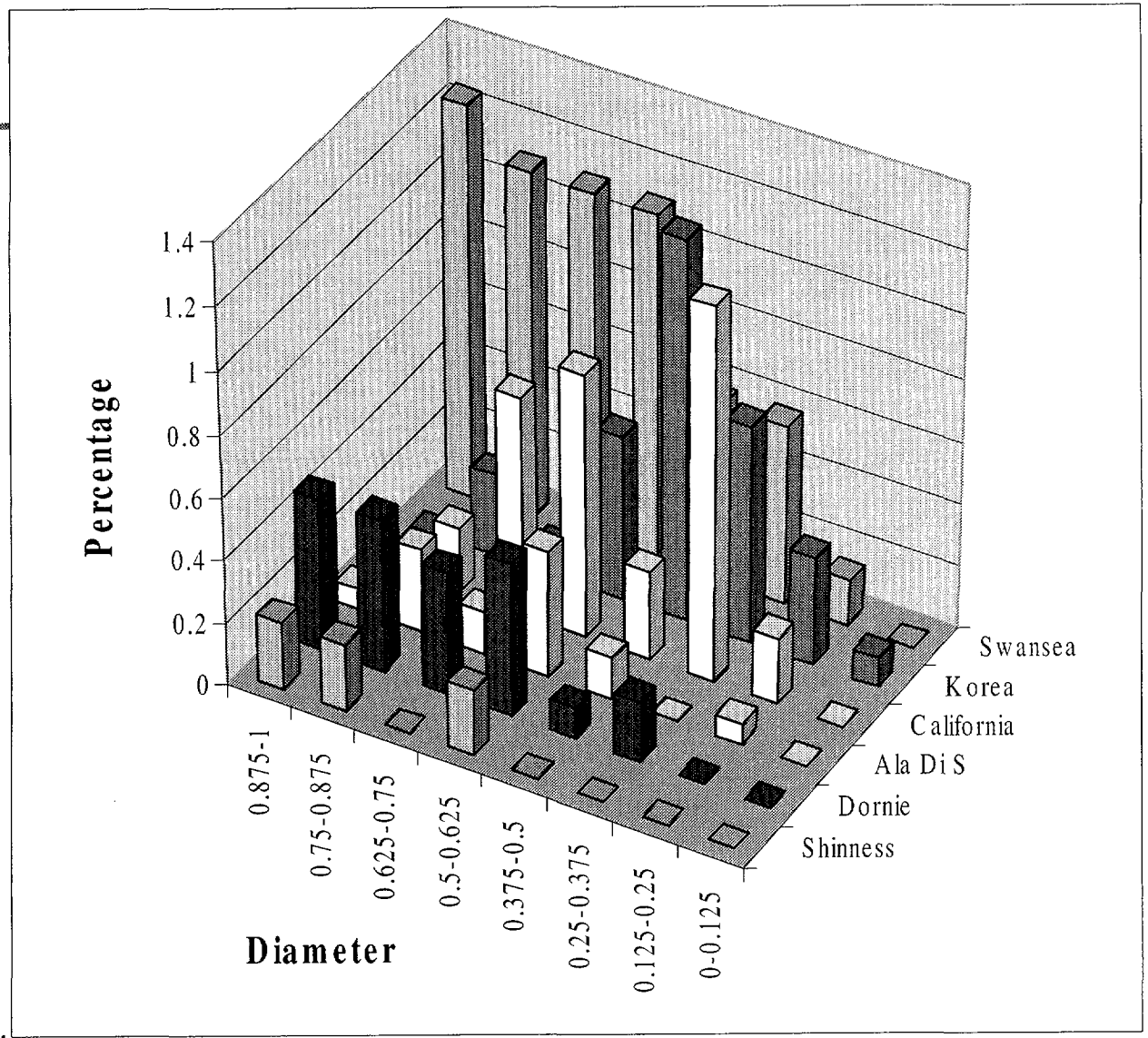
Jamestown Tremolite: L & D distribution



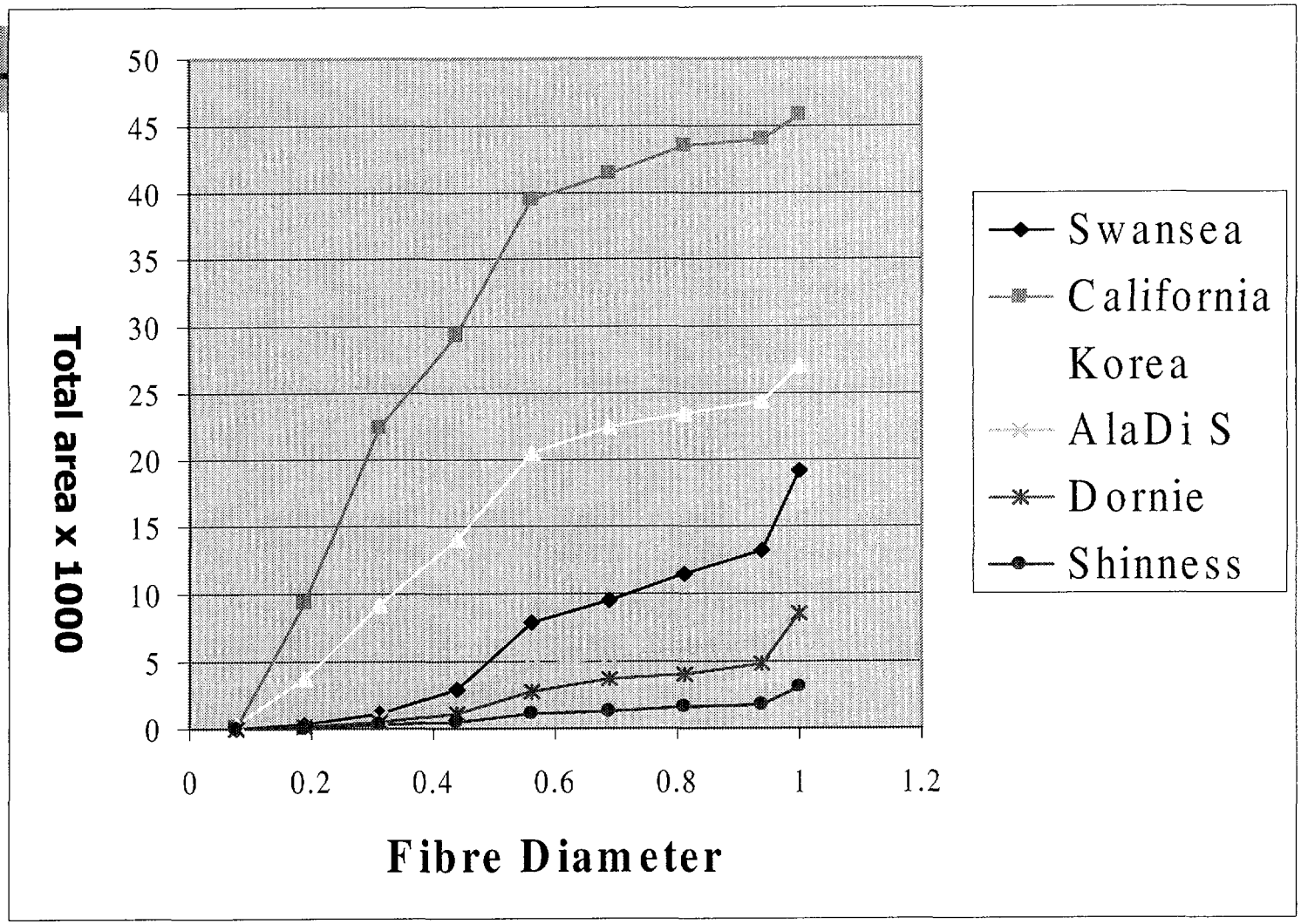
Shinness Tremolite L & D Distribution



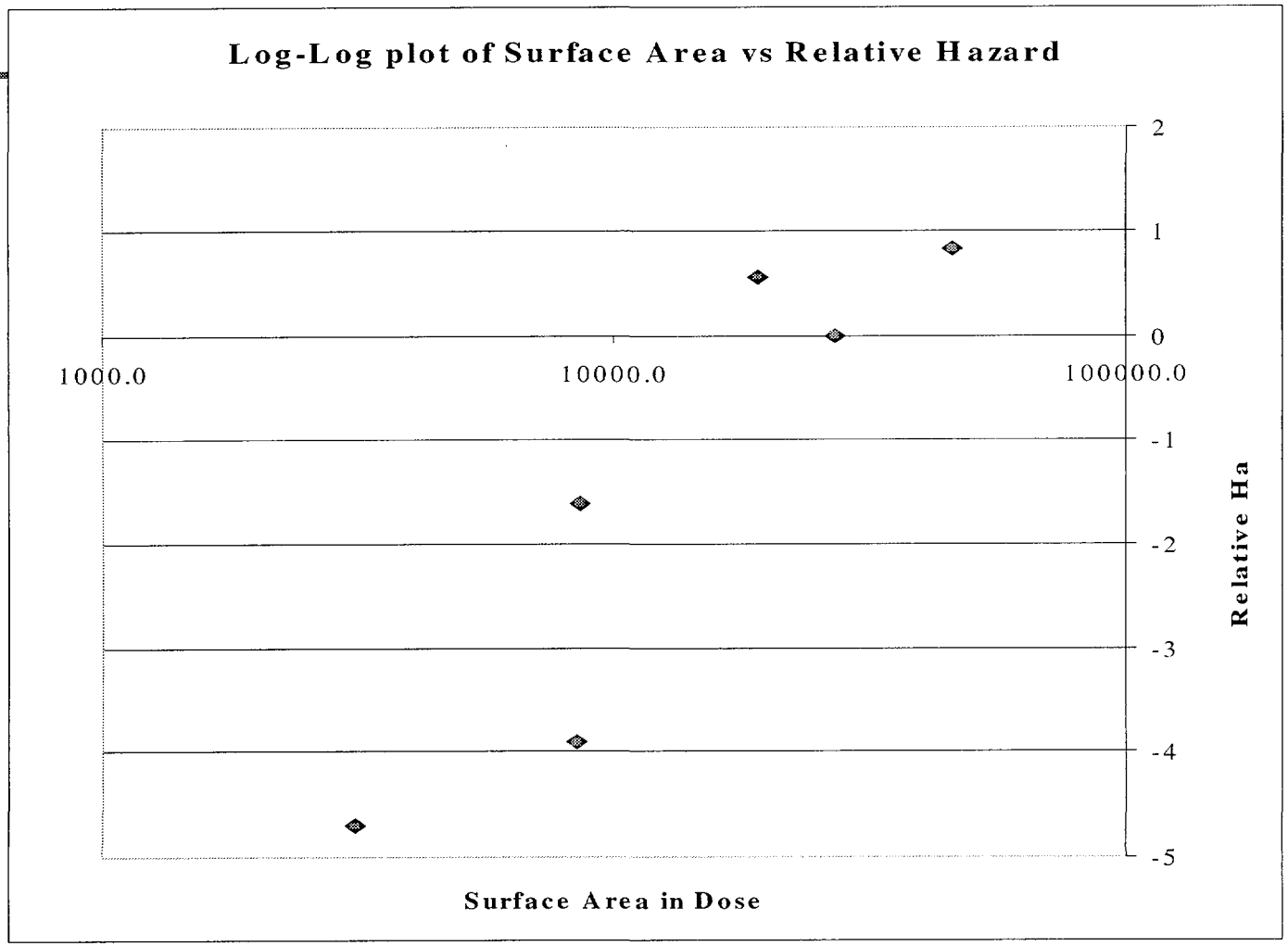
Fibres longer than 10 microns



Tremolites: Surface area of fibres in dose



Log-Log plot of Surface are vs Hazard



Mineral Properties to distinguish asbestos

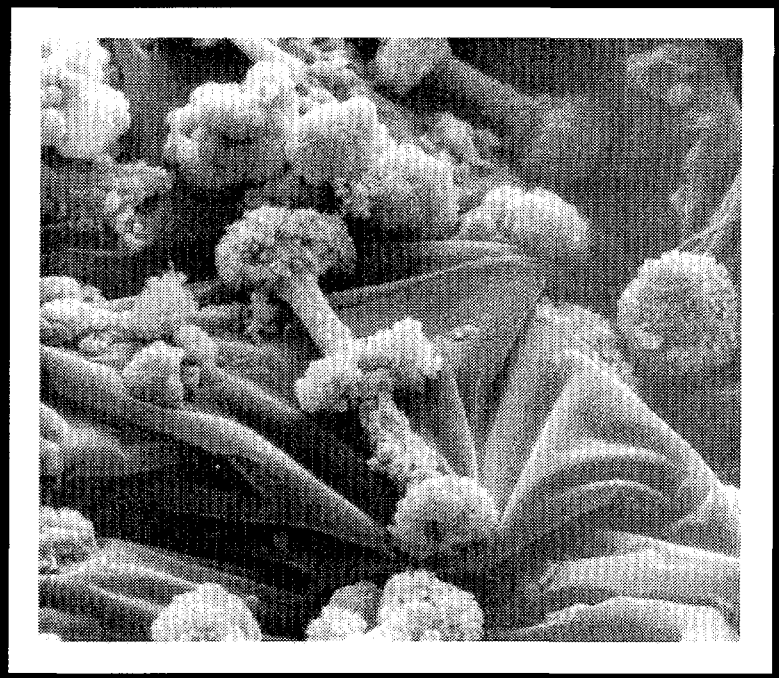
- Morphology/habit
- Polarised light microscopy
- Chemistry
- Ultra-structure
- Size and shape of particles

Airborne dusts:

- Identification criteria for asbestos fibres in airborne dust samples
- Appropriate chemistry/optical properties
- Aspect ratio greater than 20:1
- Length greater than 20 microns
- Diameter less than 1 micron

Lung-retained fiber as a marker of environmental dose

Bruce W. Case



McGill

Putting it in context: investigating two (of many possible) suspect regions via lung-retained fiber

- **Known geology**
- **Asbestos mining**
- **Over 100 years of well-described exposures**
- **Lots of reliable data (more care needed in terming exposures "non-occupational" or "environmental")**
- **What has been done; what does it teach us?**

- **Known geology**
- **Asbestos mining**
- **?? Lots of potential for exposure**
- **Some data, none on lung, little reliable on air**
- **What *could* be done?**

The lung is the ultimate personal dosimeter

Serpentinite *in two locations*

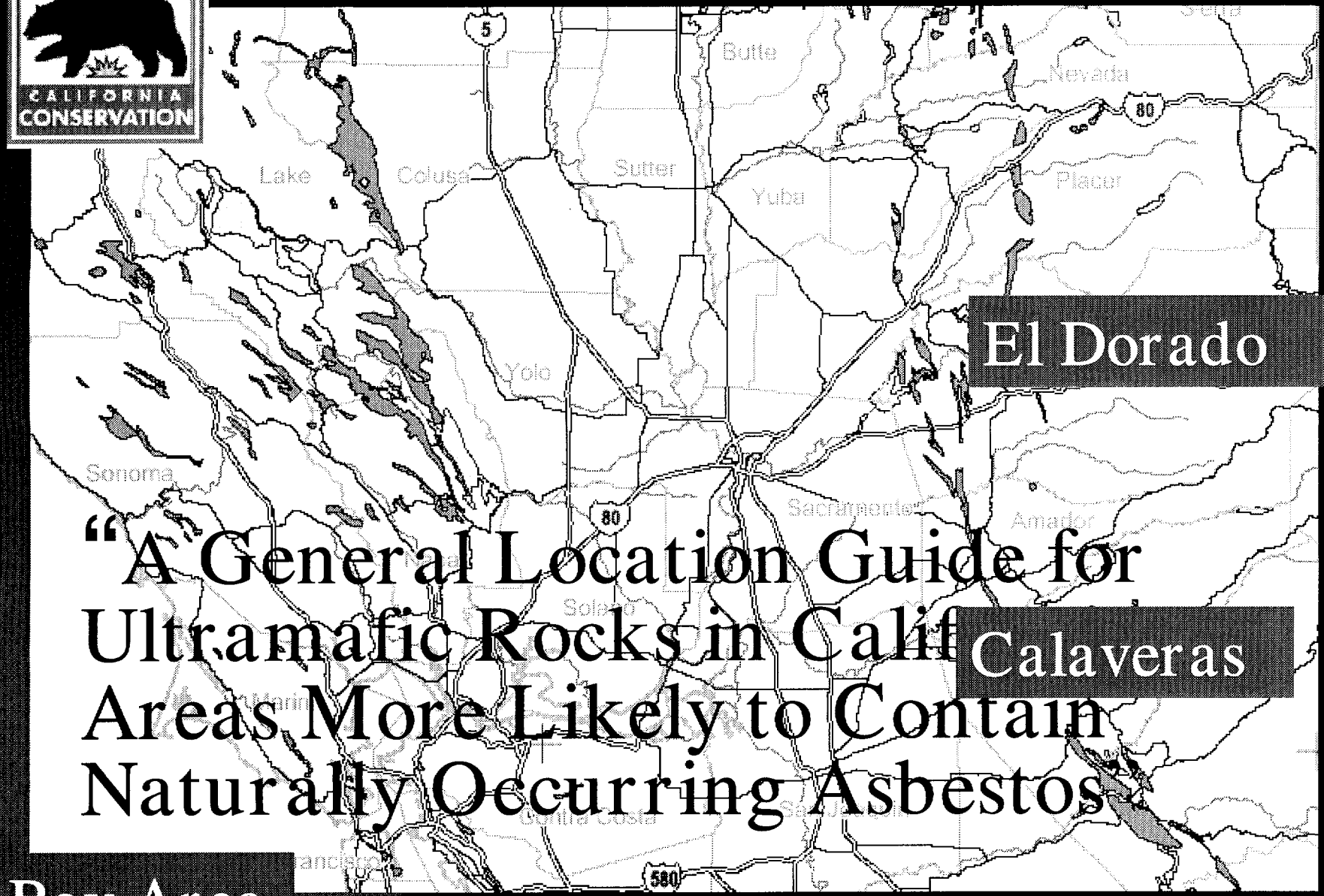
- **Serpentinite: Serpentinite is a rock consisting almost entirely of one or more serpentine minerals … not identified as separate rock units on these maps *but likely to be found within areas of ultramafic rock.***

Serpentinite *in two locations* [1]

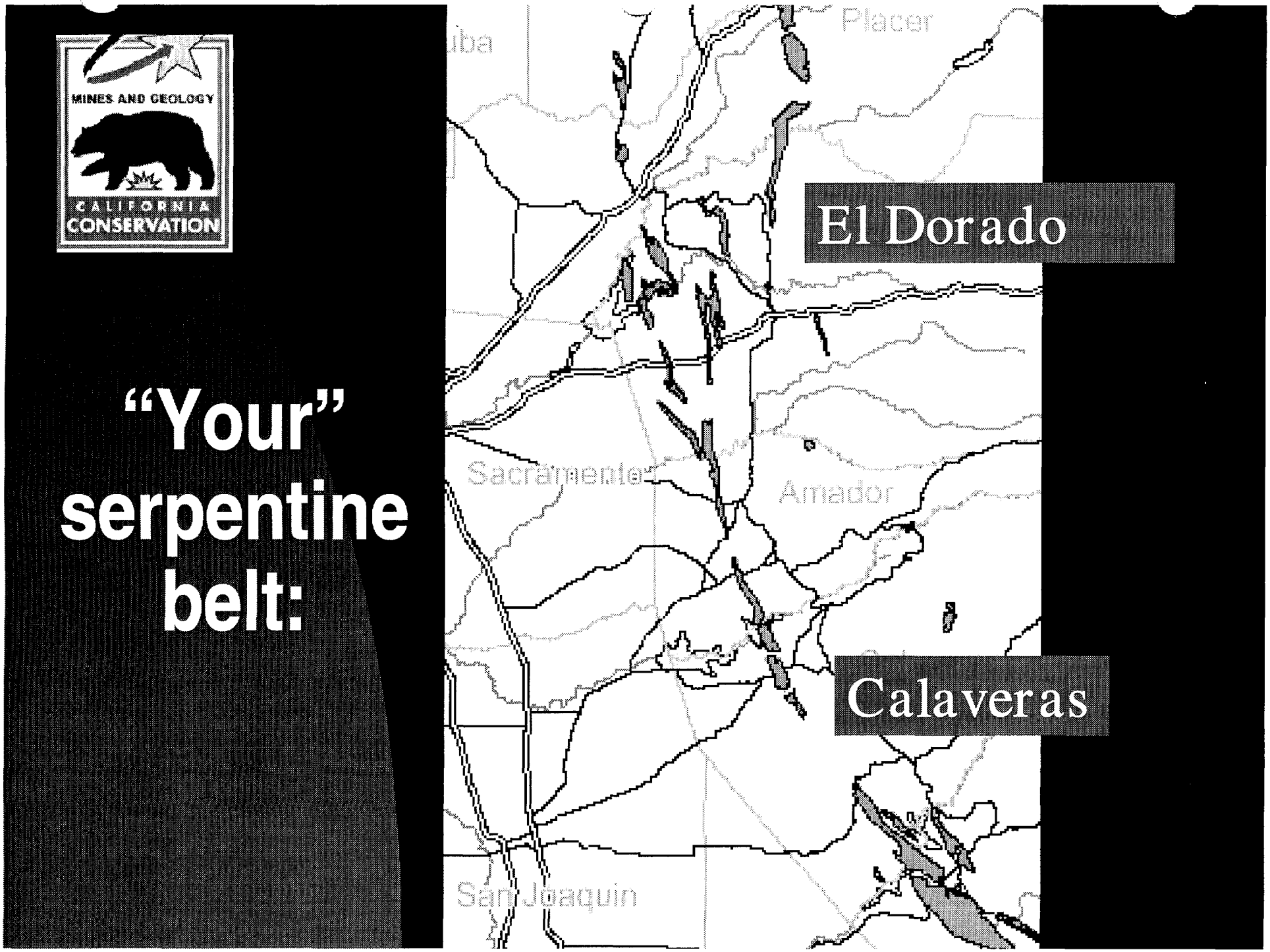
- Small amounts of chrysotile asbestos are common in serpentinite.
- because chrysotile is one of the serpentine group minerals.
- Tremolite-actinolite asbestos (amphibole asbestos) may also occur with serpentinite, but such occurrences are less common than chrysotile asbestos.

1. Source: Cal. Dept. Conservation, Division of Mines and Geology: maps also from that source, on the web

"Your" serpentine belts:

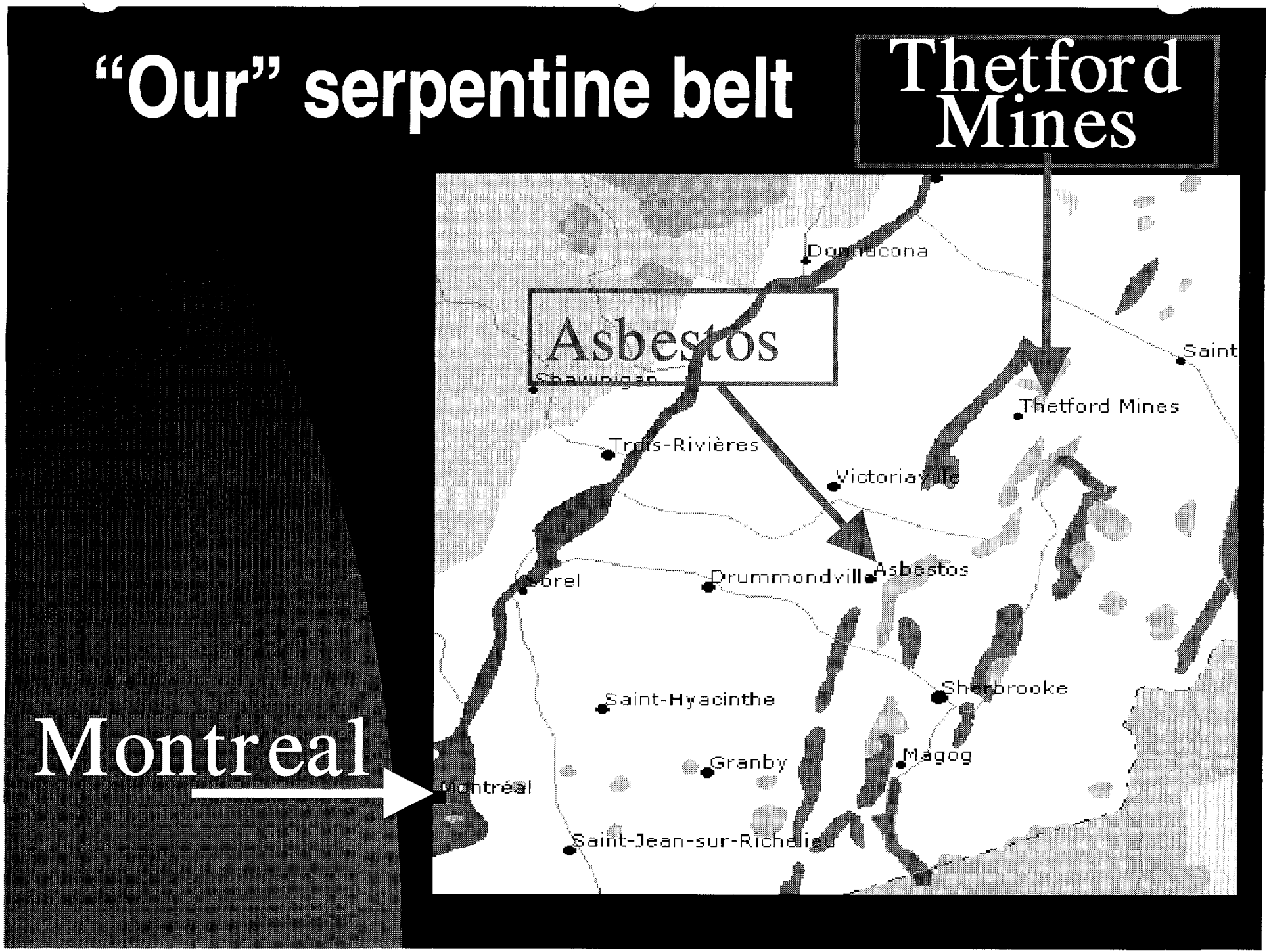


"A General Location Guide for Ultramafic Rocks in Calif Areas More Likely to Contain Naturally Occurring Asbestos"

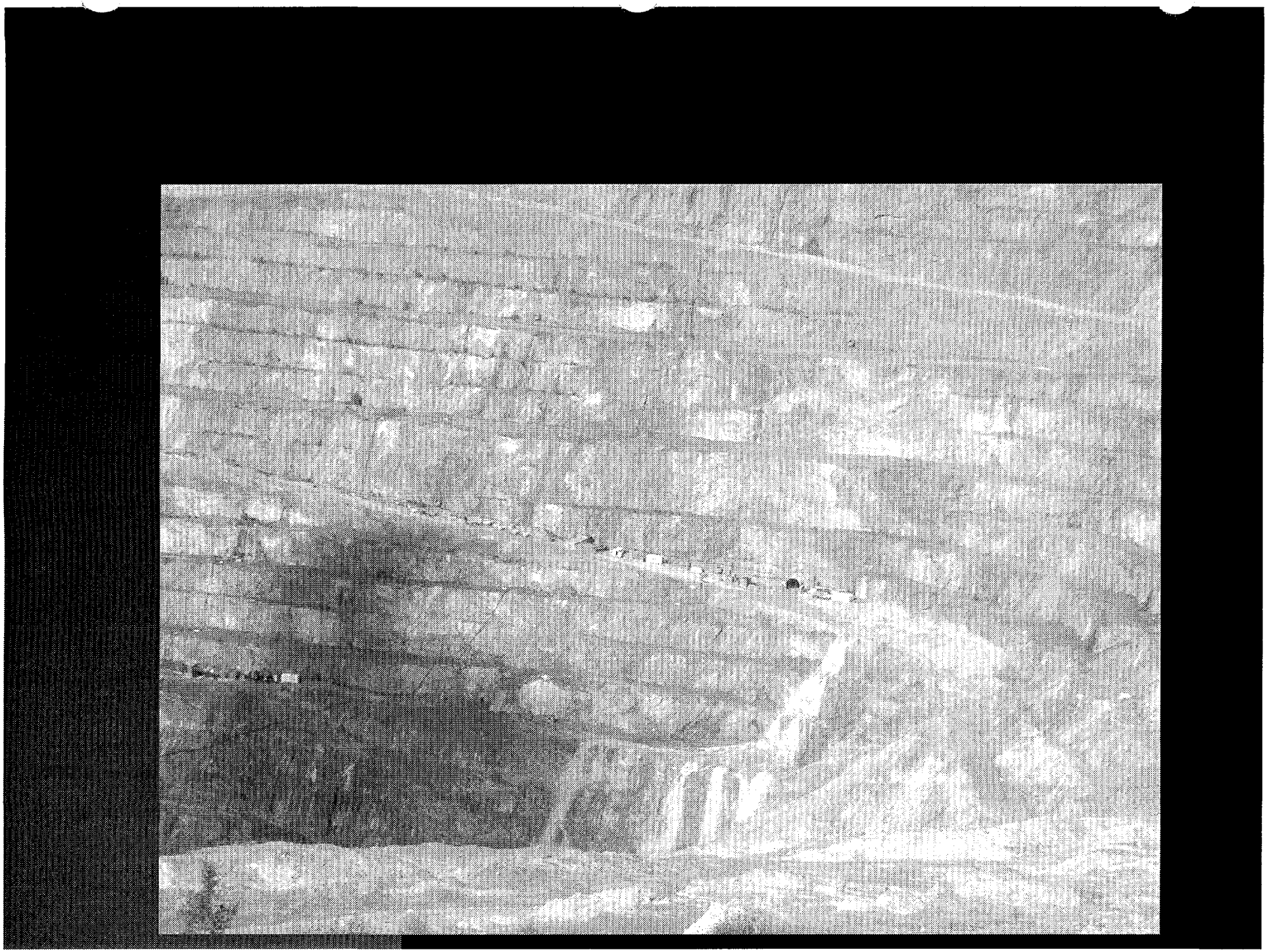

MINES AND GEOLOGY
CALIFORNIA
CONSERVATION
"Your" serpentine belt:
Placer
El Dorado
Sacramento
Amador
Calaveras
San Joaquin

"Our" serpentine belt

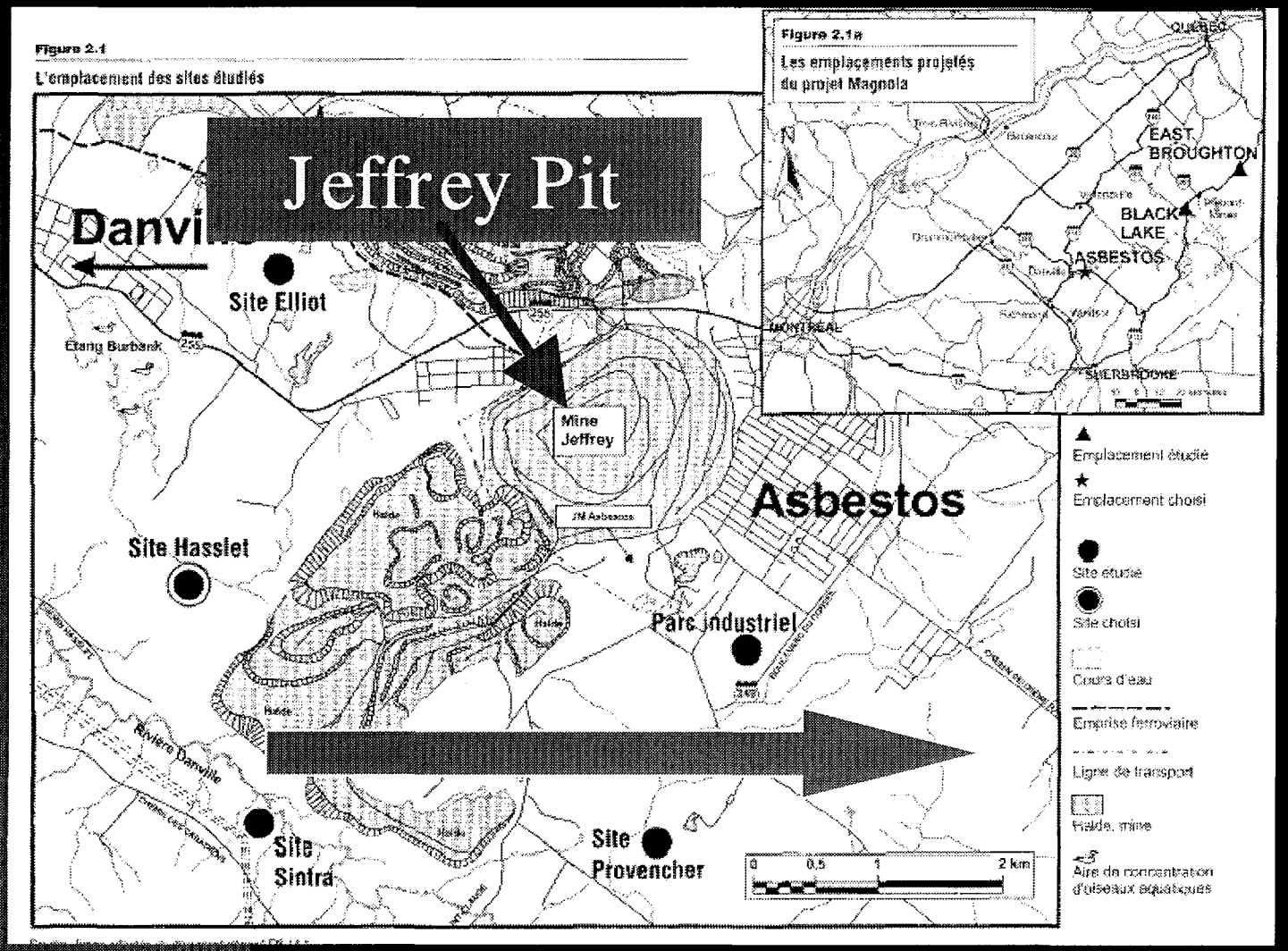
"Our" serpentine belt



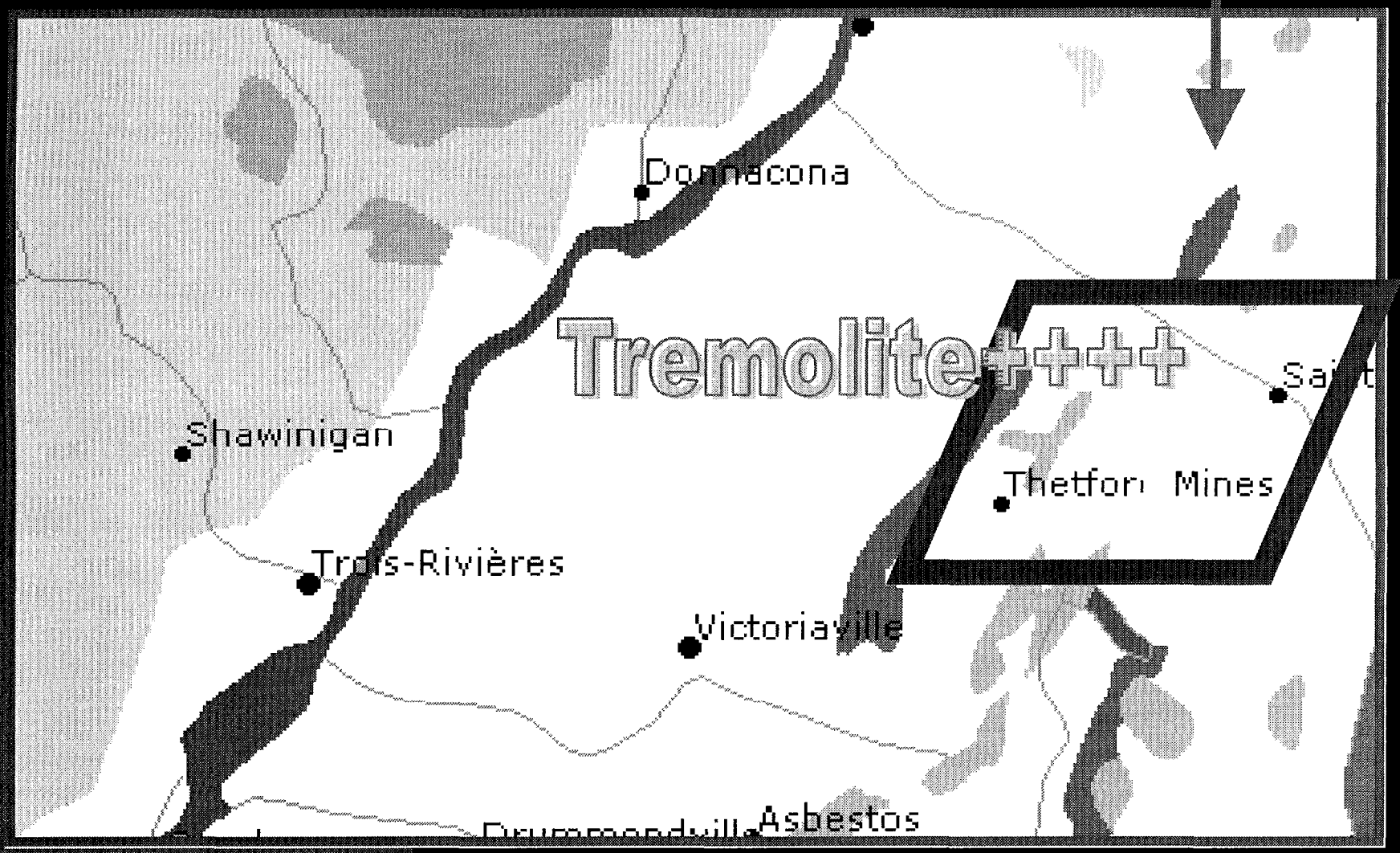
Asbestos: Jeffrey Pit: *(> 1 mile across)*



Asbestos, Quebec



Thetford Mines, Quebec



As elsewhere, the distribution of tremolite is heterogeneous.

What was/is there to look for? *

1. Asbestos "bodies" (AB) in sputum.
2. AB (and fibres?) in broncho-alveolar lavage (BAL).
3. Lung-retained asbestos fibers (generally using one or more flavors of electron micrioscopy).

* In lung digestate

The big advantages of internal dose study

1. Don't have to worry if relevant to human exposure!
2. Don't have to worry if respirable (and therefore diameter not a concern, except for resolution)
3. Generally, don't have to worry whether fibre is "biopersistent"...

Some disadvantages of internal dose study

1. Lung-retained fibers do not have "product id" stamped on them (with a few possible exceptions!)
2. Even if they did, they still would not have a "date of deposition" stamp
3. Although the presence of a fiber type guarantees its biopersistence, it does not always tell is "if it is asbestos".
4. Hence, we still have to make some decisions for risk assessment.

Is this tremolite ("T") asbestos?

Some ambiguities of internal dose study *

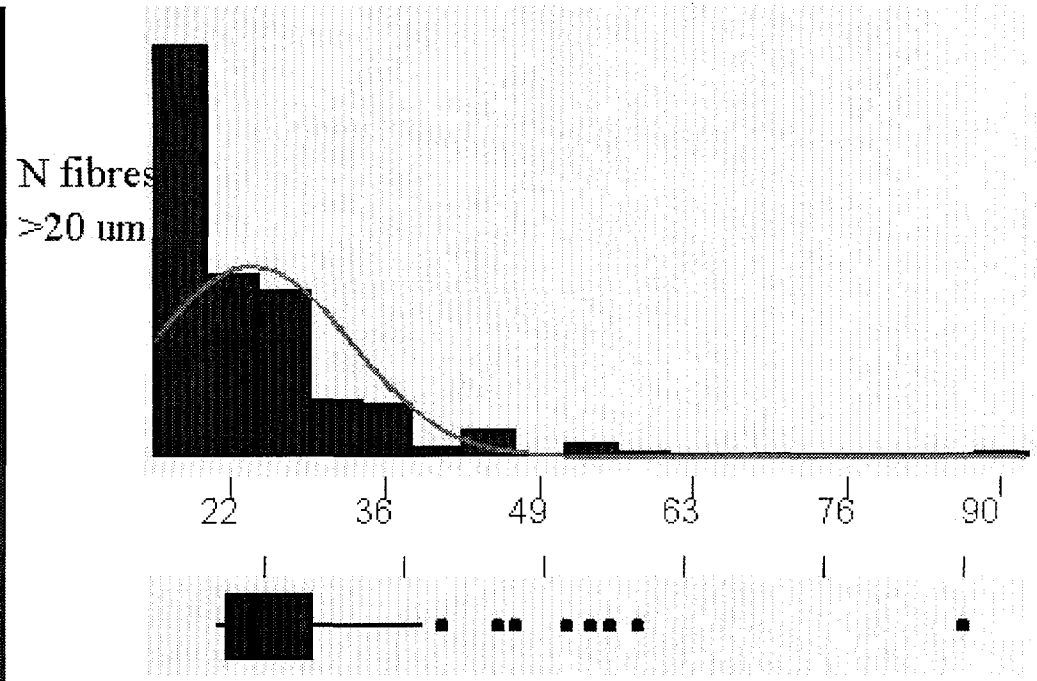
1. A decision must be made on a rational basis as to *which fiber lengths (or size distributions) to count*

2. There are technical differences introduced by differences in procedures (but these are probably overstated)

3. A principal decision has to be made upfront as to which equipment (TEM, SEM, etc.) to use.

These are not "problems" but decisions to be made by the investigators; it may not be necessary to decide which is "best"

Which fiber length(s) to count? (255 chrysotile fibers in lungs of 43 textile workers: range 18 to 90 micrometers, TEM/EDS)



Anderson-Darling Normality Test

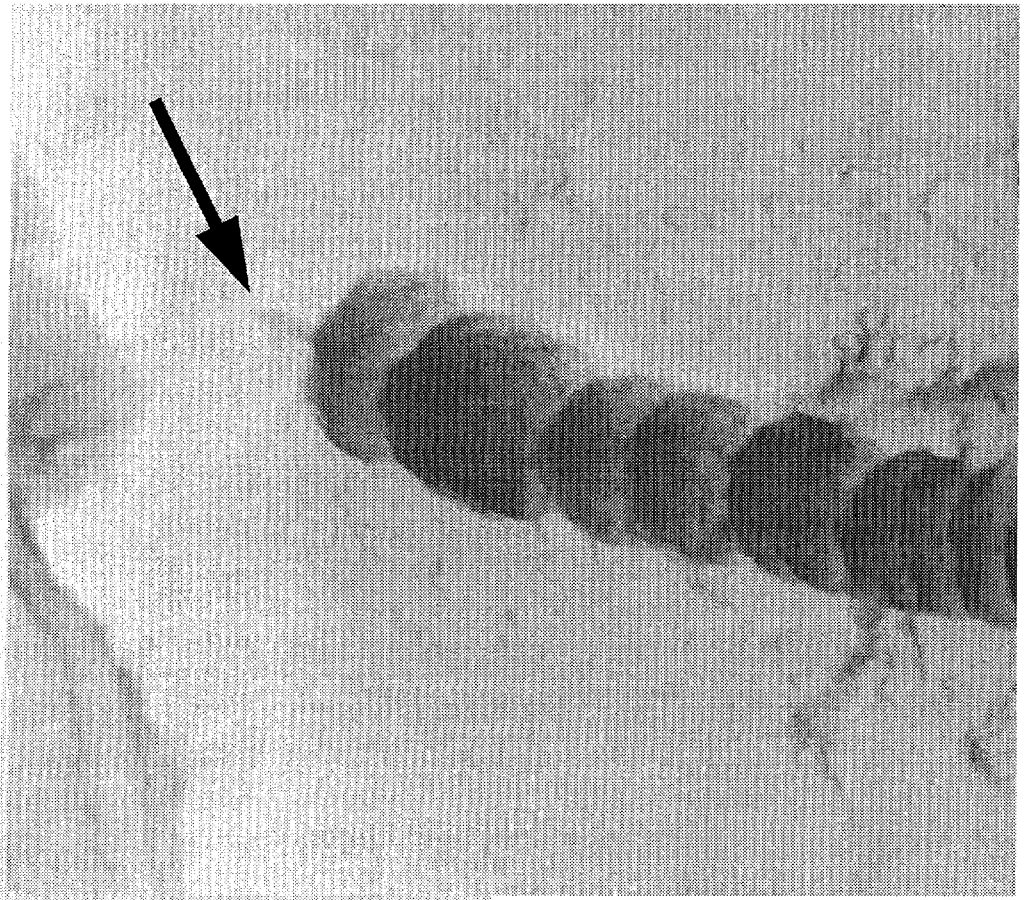
A-Squared:	19.921
P-Value:	0.000
N	255
Minimum	18
Median	21.6
Maximum	90

95% Confidence Interval for Median

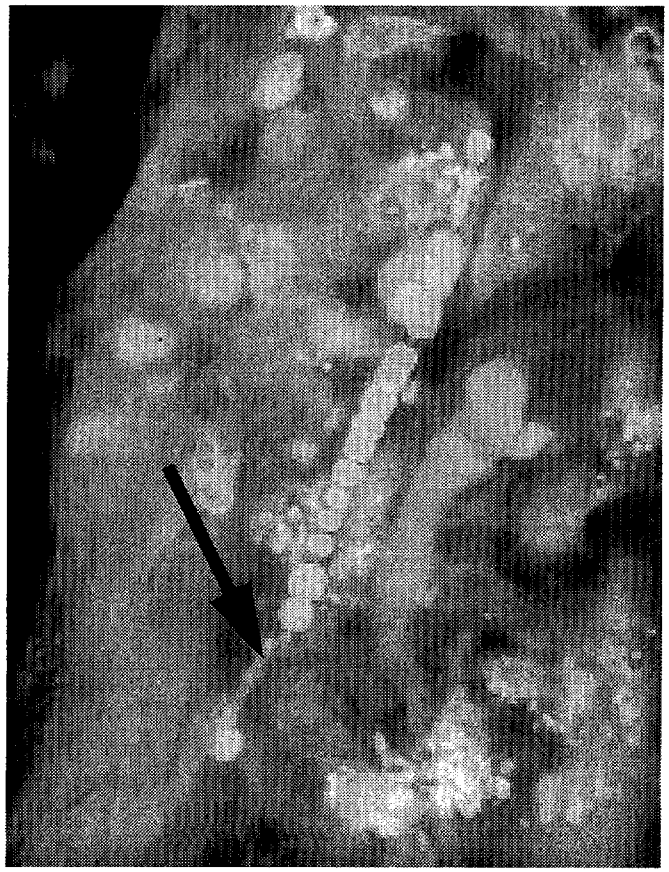
19.8 um	22.1 um

Case B et al. *Inhalation Toxicology* 2000

Asbestos Bodies

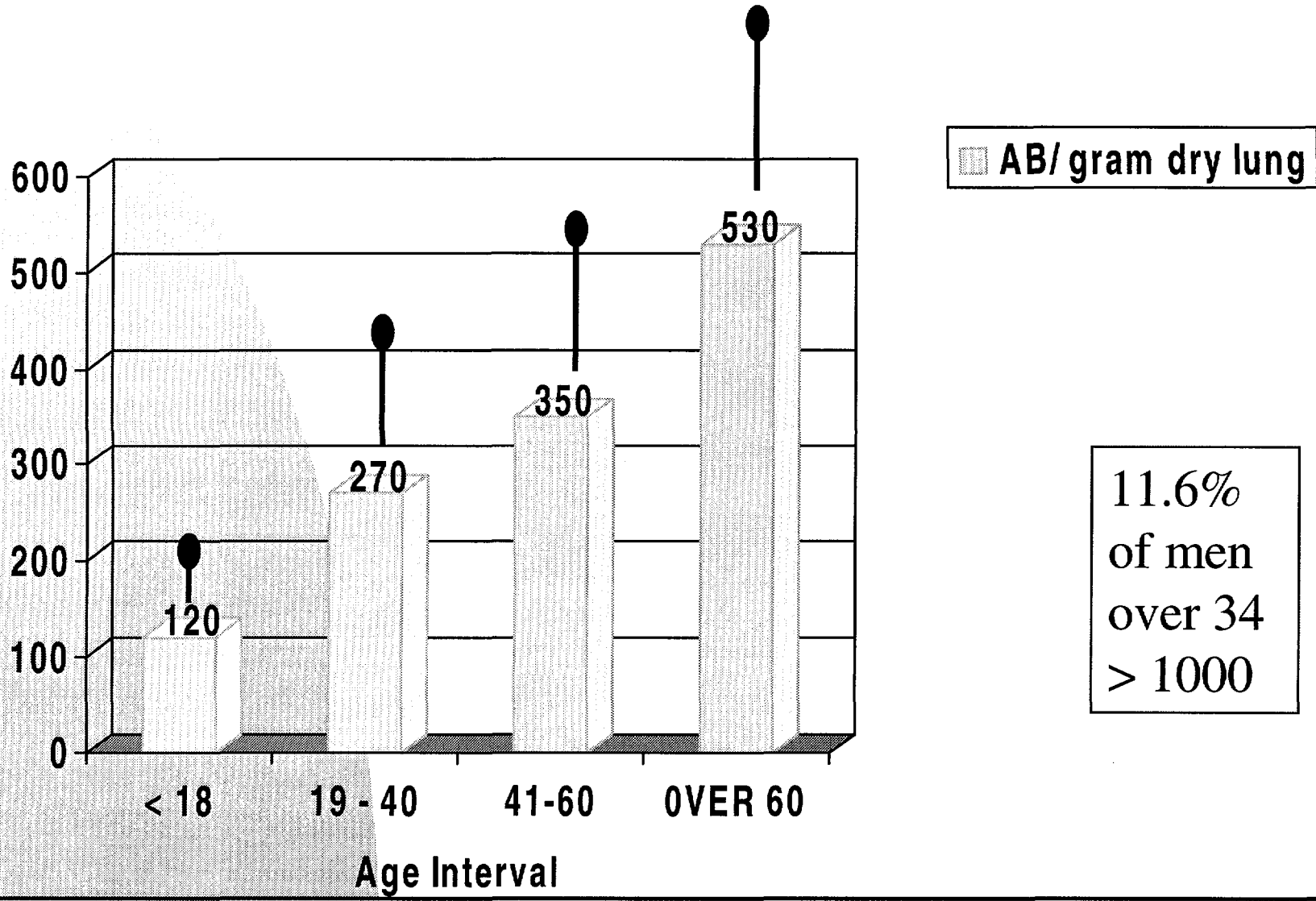


By scanning electron Microscopy



Light Microscopy

Asbestos bodies in *lung*: the Canadian series of accident victims*



11.6% of men over 34 > 1000

* Case, Sebastian, McDonald J. Arch Env Health 1988, 43:178

Sputum AB in ASBESTOS (A) and THETFORD MINES (TM):

SUBJECTS	N (age, smoking)	N adequate	N positive
Miners/ Millers (A)	55 (57, > 80%)	32 (58%)	9 (17%)
Miners/ Millers (TM)	89 (56, 87%)	42 (48%)	10 (12%)
Women (A) > 50% exposed	30 (40, 33%,)	8! (26%)	0
Women (TM) > 50% exposed	21 (58, 33%)	10 (48%)	3 (14%) (exposed non-smokers)

Could this be used to assess people in an area like El Dorado?

1. Yield very low, but single morning sputum in youngish nonsmokers
2. On the other hand, the Quebec groups were definitely exposed
3. Sequential sputums better? Restrict to smokers?
4. Ethical concerns – should residents be approached? Could sputum be saline–induced?

2. BA Lavage (in living patients)

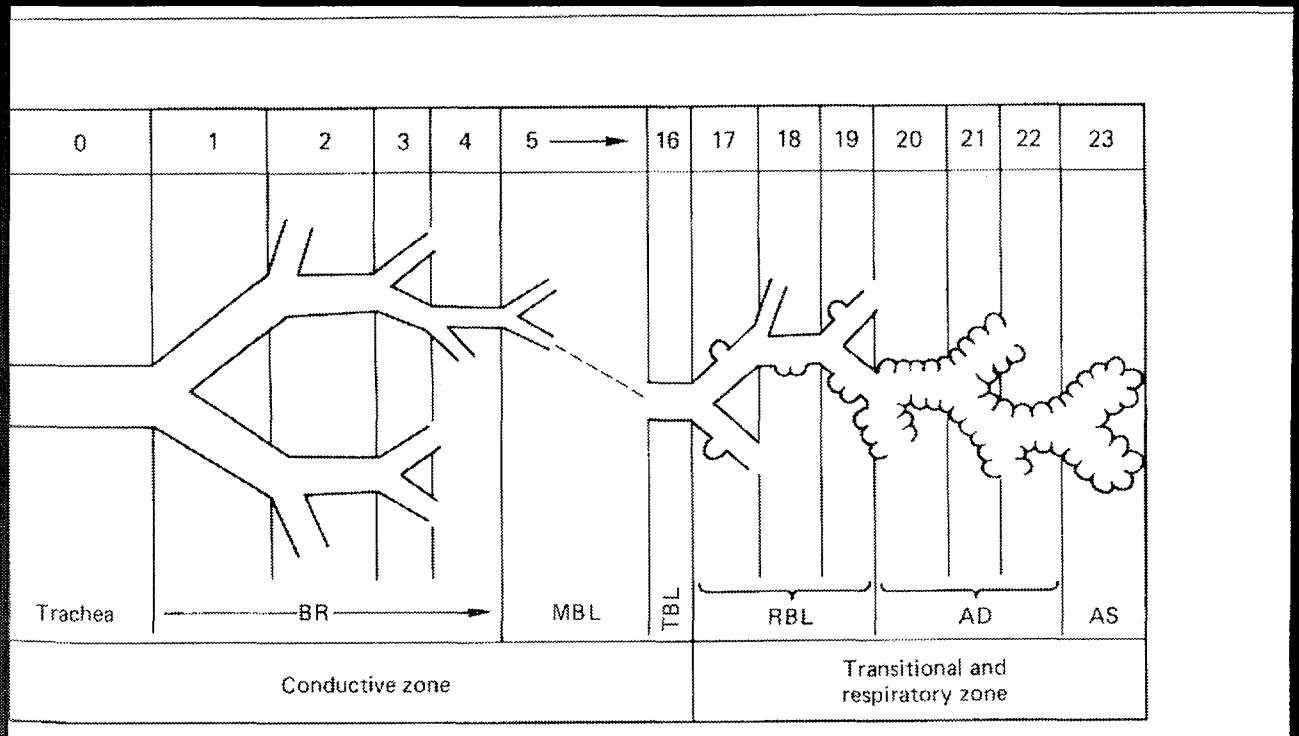
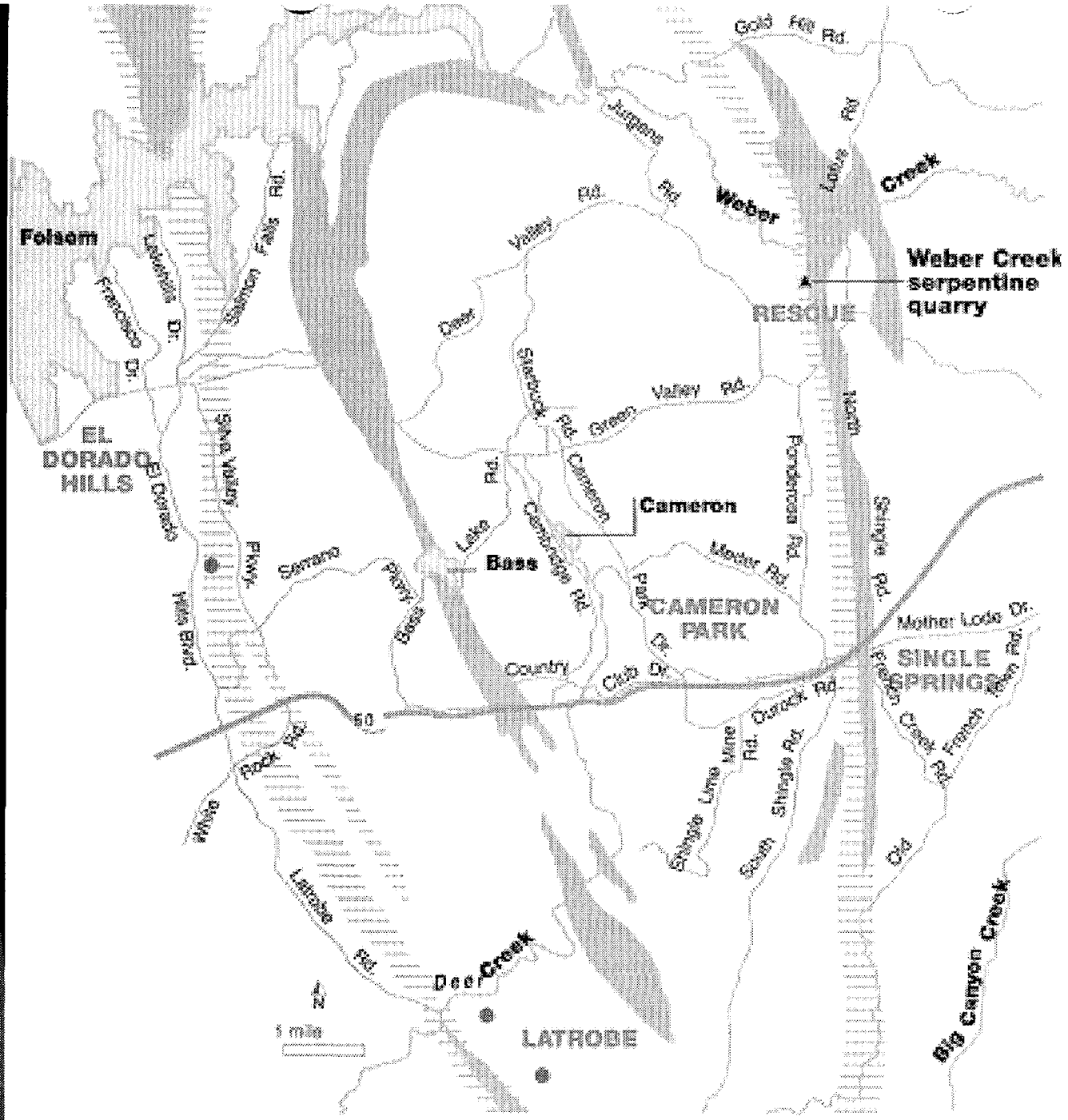


Figure 1.2 Conducting airways and respiratory unit (not to scale) as represented by Weibel's idealized system of generations branching from the trachea by symmetrical dichotomy. Numbers of generations are shown at the top. BR = bronchi, MBL = membranous bronchioles, TBL = terminal bronchiole, RBL = respiratory bronchioles, AD = alveolar ducts, AS = alveolar sacs.

BAL for exposure assessment: is it possible?

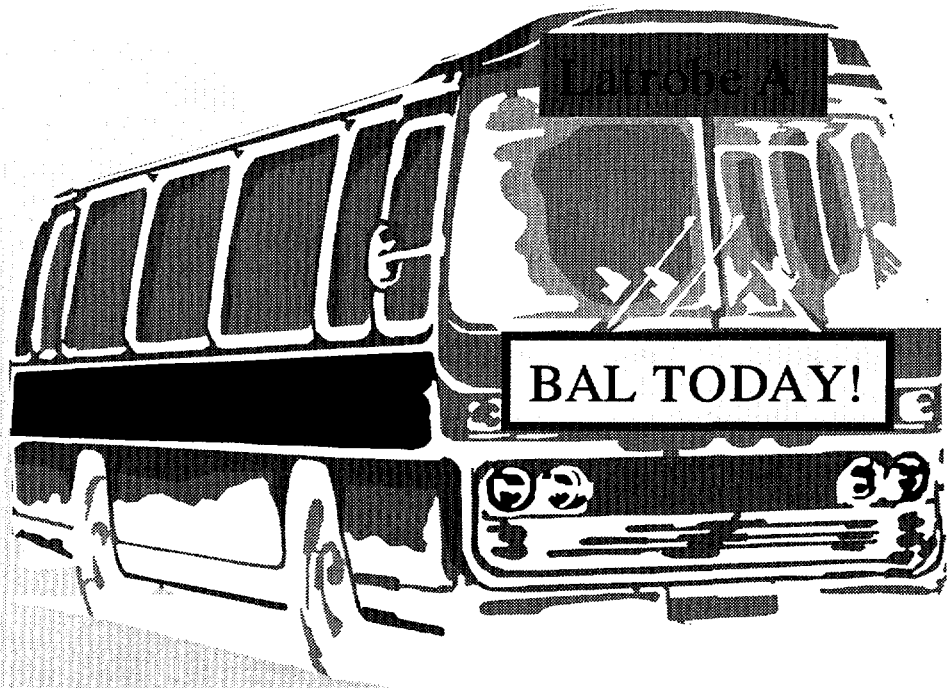
1. Yes – volunteers are often used for this uncomfortable procedure, and
2. One group in Belgium assesses BAL for Asbestos Bodies *routinely on every patient (1992-97 (N=1800) Dumortier et al. 2001)*
3. *The work done to date suggests that there is a rough correspondence* between a level of one (1) AB per ml BAL fluid and 1000 AB per gram dry lung by traditional method

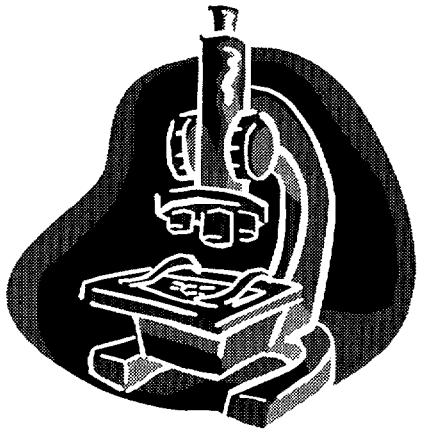
El Dorado



©1998, The Sacramento Bee
(Published March 29, 1998)

BAL for exposure assessment: is it possible?

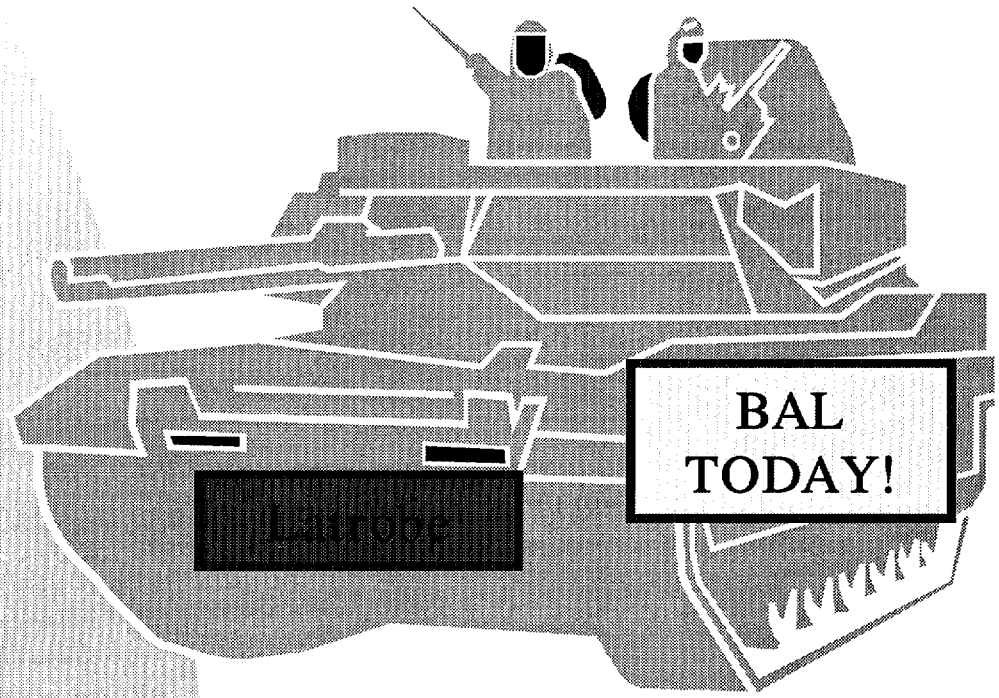




BAL for exposure assessment: is it possible?

1. So, let's do it…*not so fast!*
2. Problem with "volunteers" for such studies
3. Ethical problems:
    1. In even *approaching* people?
    2. In getting informed consent *from people who are not sick to do something that is "not necessary"*

BAL for exposure assessment: is it possible?



A *sampling* might be possible, but how representative would it be?

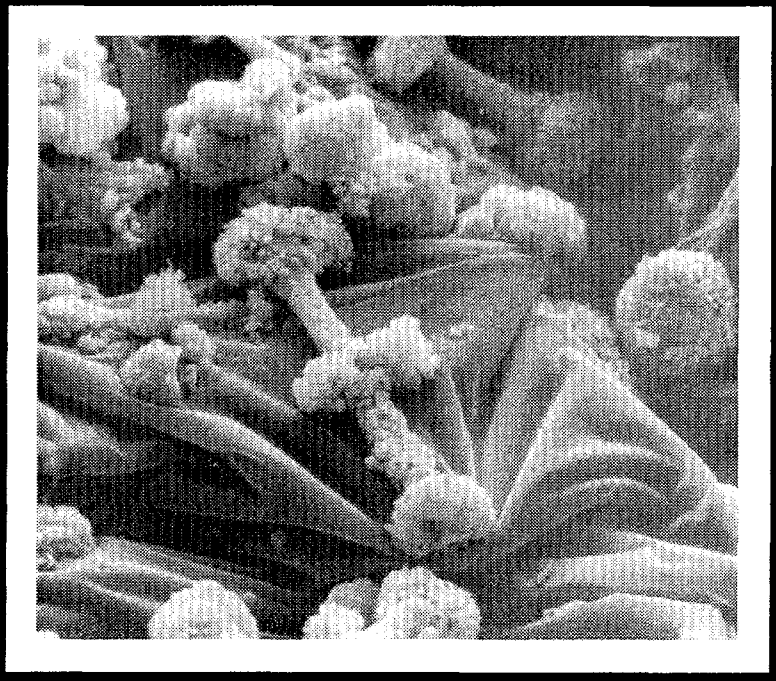
Method 3: analysis of lung digestate

- **Tried and true; methodological difficulties are largely confined to between-lab comparisons**
- ***As long as a lung-retained study of asbestos (AB and fibers) uses accepted epidemiological principles, it is likely to produce a usable and interpretable result: data should include all fiber parameters but should be limited to "longer" fibers)***

Method 3: analysis of lung digestate

- ***At the very least, analysis + questionnaires will tell us what exposures existed for this group.***

Identifying exposure by electron microscopy



Important not to confuse this type of study with medico-legal or compensation case series

- Studies must be to the degree possible population-based (some selection bias is unavoidable).
- Much of the literature is from legal/ comp cases; while it may help us with methods it cannot be used to (for example) establish background values or cause.

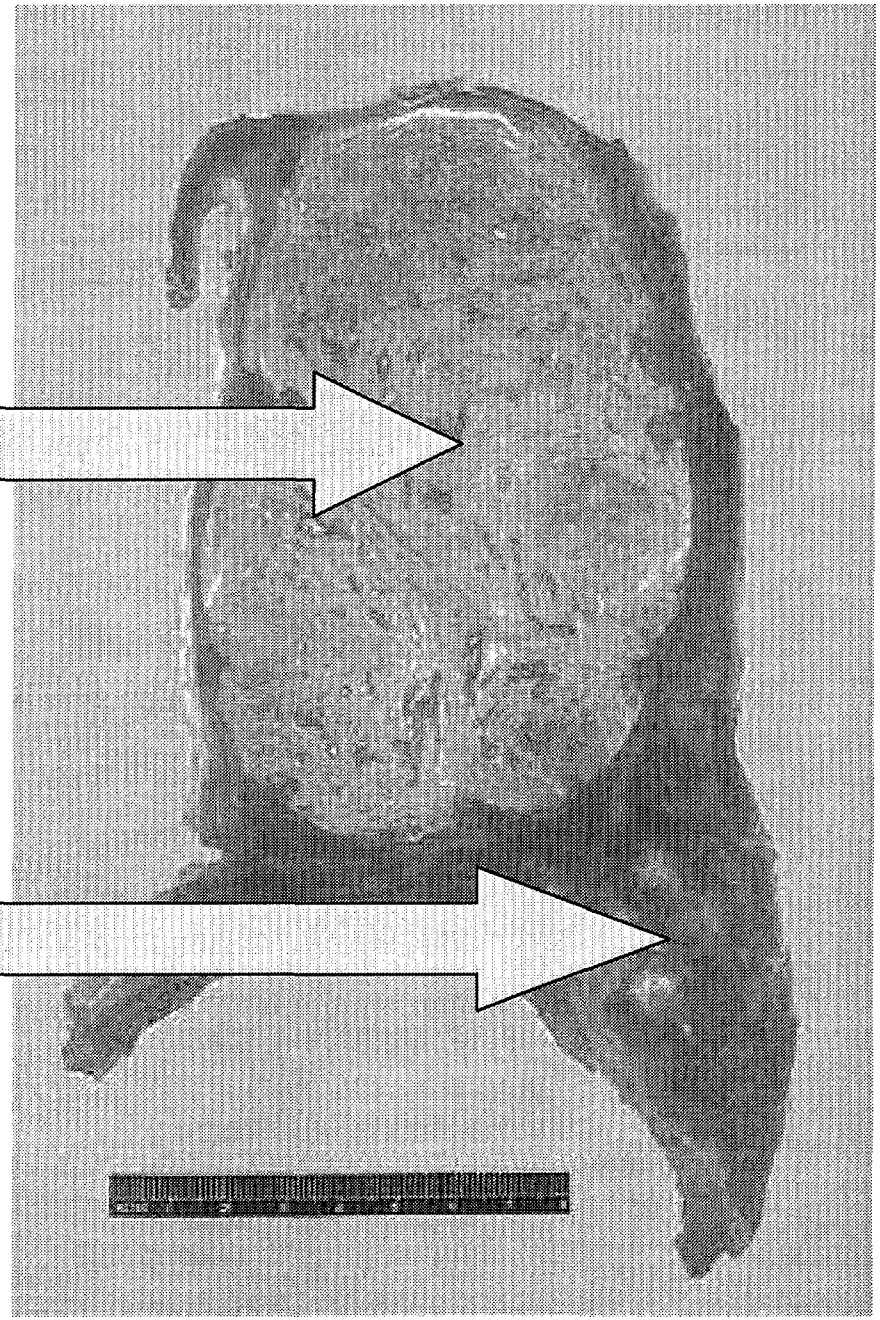
Unfortunately, there are only two possible sources of lung tissue:

- Autopsy lung tissue (including, perhaps especially, from coroner's cases)
- Lung cancer surgical cases (may not be as bad as it sounds, but definite bias toward smoking and any other factors that smoking may represent (class, education…))

two possible sources of lung tissue: continued

- Because most lung cancer cases are not related to asbestos exposure, this is not a major problem, although ideally questionnaire approach should be used to exclude ANY case with possible occupational asbestos exposure

One word on sampling: *only lung is valid*



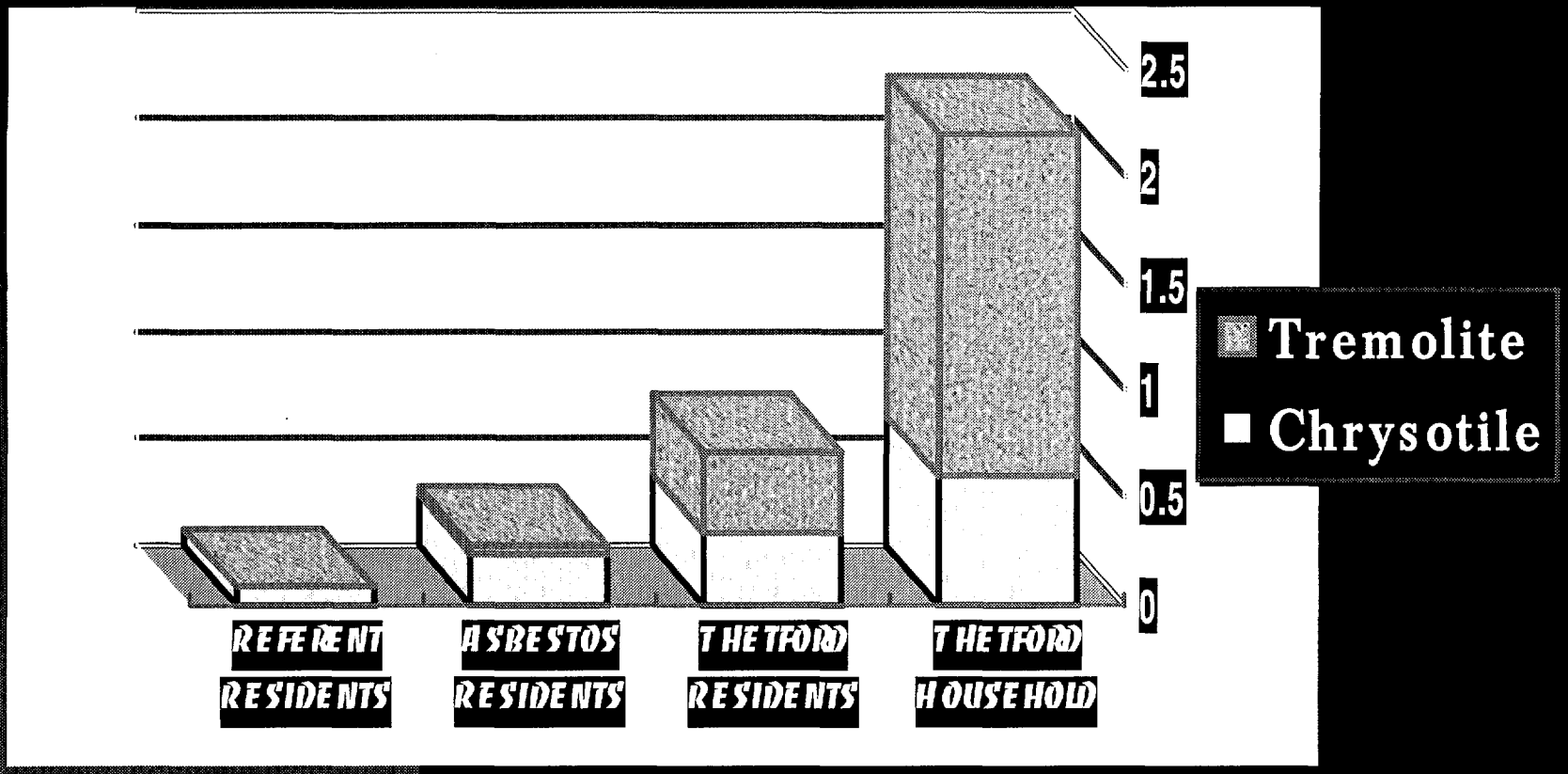
Thetford Region: by questionnaire, using paraffin blocks

Two Studies

	Referents (N=14)	Neighbor-hood (14)	Domestic ? (N=8)	Domestic (N=10)
Asbestos Bodies	**80**	1560	2360	4260
Chrysotile	0	0.33	0.23	**1.60**
Tremolite	0	0.37	0.19	**1.64**
% Tremolite	0	40%	30%	40%

Case BW. Ann NY Acad Sci 1991; 643:491-504

Lung burden of mining region residents in Asbestos and Thetford Mines (wet tissue)



Can this be done in El Dorado?

1. Yes, if indicated and if practical…
2. - use hospital directories OR
3. - use pathologist inquiries OR
4. - use coroners

must have informed consent

Can this be done in El Dorado?

Whichever source used,

- controls must be appropriate
- lifetime residential histories and occupational histories are ideal
- just like disease, exposure can be "mapped" (GIS)


Shawinigan
Trois-Rivières
Victoriaville
Drummondville
Asbestos
Sherbrooke
Saint-Hyacinthe
Granby
Magog
Placer
El Dorado
Sacramento
Amador
Calaveras
San Joaquin

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Carcinogenicity of Asbestos

Differences by Fiber Type?

John M. Dement, Ph.D., CIH

Duke University Medical Center
Durham, N.C.

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Fiber Types of Primary Interest

- Serpentines
  - Chrysotile
- Amphiboles
  - Amosite
  - Crocidolite
  - Tremoilte

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Cancer Sites Considered

- Lung Cancers (All Cell Types)
- Mesothelioma
  - Pleural or Peritoneal

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Guidance for Causal Inference

Bradford Hill (1965)

- **Strength of the association?**
- **Consistency of the association?**
- **Specificity of the association?**
- **Biological gradient (exposure-response)?**
- **Temporality of exposure and disease?**
- **Biological plausibility?**

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Causal Inference - Lung Cancer

Guidance Criteria	Amphiboles	Chrysotile
Strength	+++	+++
Consistency	+++	++
Specificity	–	–
Biological Gradient	+++	+++
Temporality	+++	+++
Biologic Plausibility	+++	+++

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Causal Inference - Mesothelioma

Guidance Criteria	Amphiboles	Chrysotile
Strength	+++	++
Consistency	+++	++
Specificity	+++	+++
Biological Gradient	+++	++
Temporality	+++	+++
Biologic Plausibility	+++	+++

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Slide 7

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Summary of Carcinogenicity Data by Fiber Type

- Epidemiological data fully support increased risk for lung cancer and mesothelioma for amphiboles and chrysotile.
- Animal bioassay, including inhalation studies, have shown all fiber types to increase the risk of lung cancer and mesothelioma.
- The lung cancer risk for chrysotile is at least as high as that observed for amphiboles.
- While chrysotile causes mesotheliomas, epidemiological data show the proportional yield (as a % of deaths) to be less than observed for amphiboles.
- No scientifically defensible thresholds have been established for lung cancer or mesothelioma.

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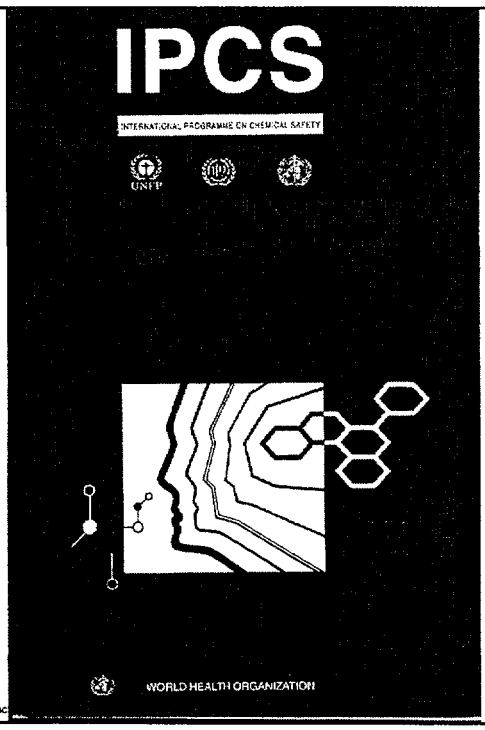
Slide 8



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WHO, IPSC Chrysotile Report
Environmental Health Criteria 203, 1998

"Commercial grades of chrysotile have been associated with an increased risk of pneumoconiosis, lung cancer and mesothelioma in numerous epidemiological studies of exposed workers"

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WORLD TRADE ORGANIZATION

WT/DS135/R
18 September 2000

(00-3353)

EUROPEAN COMMUNITIES – MEASURES AFFECTING ASBESTOS AND ASBESTOS – CONTAINING PRODUCTS

Report of the Panel

The report of the Panel on *European Communities – Measures Affecting Asbestos and Asbestos – Containing Products* is being circulated to all Members, pursuant to the DSU. The report is being circulated as an unrestricted document from 18 September 2000 pursuant to the Procedures for the Circulation and Derestriction of WTO Documents (WT/L/160/Rev.1). Members are reminded that in accordance with the DSU only parties to the dispute may appeal a panel report. An appeal shall be limited to issues of law covered in the Panel report and legal interpretations developed by the Panel. There shall be no *ex parte* communications with the Panel or Appellate Body concerning matters under consideration by the Panel or Appellate Body.

A Free sample background from www.pp Note by the Secretariat: This Panel Report shall be adopted by the Dispute Settlement Body (DSB) within 60 days after the date of its circulation unless a party to the dispute decides to appeal or the DSB decides by consensus not to

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World Trade Organization
Decision of September 18, 2000

The "carcinogenicity of chrysotile fibers has been acknowledged for some time by international bodies," the panel noted. "This carcinogenicity was confirmed by the experts consulted by the panel, with respect to both lung cancers and mesotheliomas ... . We therefore consider that we have sufficient evidence that there is in fact a serious carcinogenic risk associated with the inhalation of chrysotile fibers."

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Developments During & After WTO Deliberations on Chrysotile

- Canada argued that risks for chryostile exposure should not be based on results for textile studies --- in any way.
- Case et. al. provided a draft report to WTO concerning fiber burden analyses of textile workers compared to chrysotile miners and millers.
- Case et. al. analyses subsequently published with arguments supporting Canada's position.

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MORTALITY AMONG CHRYSOTILE ASBESTOS TEXTILE WORKERS

- 3022 production workers employed at least 1 month between 1940 and 1965.
- Follow-up through December 31, 1990.
- SMRs based on age, race and calendar time specific death rates for U.S. using NIOSH life table.
- Nested case-control analyses for lung cancer.
- Exposure-response modeling for lung cancer & asbestosis.

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Mortality by Major Disease Groups
Asbestos Textile Workers 1940-1990

CAUSE OF DEATH CATEGORY (9th Revision ICD codes)	ALL WORKERS	
	OBS	**SMR**
ALL CANCER (140-208)	283	**1.19** (1.08 - 1.32)
HEART DISEASE (390- 398, 402, 404, 410-414, 420-429)	414	**1.22** (1.12 - 1.32)
RESPIRATORY DISEASE (460-466,470-478,480-487,490-519)	105	**1.75** (1.47 - 2.05)
• PNEUMOCONIOSIS & OTHER (470-478,494-519)	69	**3.11** (2.52 - 3.80)
ALL CAUSES	1258	**1.28** (1.21 - 1.33)

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Chrysotile Asbestos Textile Workers
Overall Cancer Mortality

CAUSE OF DEATH CATEGORY (9th Revision ICD codes)	ALL WORKERS OBS	SMR
ALL DIGESTIVE & PERITONEUM (150-159)	53	**0.86** (0.67 - 1.07)
ALL RESPIRATORY (160-165)	134	**1.99** (1.71 - 2.29)
• LARYNX (161)	4	**1.55** (0.53 - 3.55)
• TRACHEA, BRONCHUS & LUNG (162)	126	**1.97** (1.69 - 2.28)
• OTHER RESPIRATORY (160,163-165)	4	**5.04** (1.73 - 11.5)
ALL OTHER CANCERS	77	**0.87**
ALL CANCER (140-208)	283	**1.19** (1.08 - 1.32)

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LUNG CANCER EXPOSURE-RESPONSE
SRR Analyses

Cumulative Exposure (fiber-years)	Lung Cancer SRR (95% CI)
<2.7	**1.0 (Reference, SMR=1.06)**
2.7 - 6.8	**2.1 (1.1-3.8)**
6.8 - 27.4	**1.8 (1.0-3.35)**
24.4 -109.5	**2.7 (1.5-4.8)**
>109.5	**4.9 (2.6-9.0)**

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Lung Cancer Case-Control Analyses
Controlling for Mineral Oil Exposure

Cumulative Asbestos Exposure fiber/cc-years	Odds-Ratio Without Control for Mineral Oil Exposure	Odds-Ratio With Control for Mineral Oil Exposure[A]
<2.7	1.00	1.00
2.7-6.8	2.13 (1.12-4.07)	2.04 (1.07-3.90)
6.8-27.4	2.14 (1.06-4.33)	2.05 (1.00-4.13)
27.4-109.5	3.27 (1.71-6.24)	3.26 (1.71-6.22)
≥109.5	7.11 (3.51-14.40)	7.03 (3.47-14.24)

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Fiber Burden Analyses
Case et al., 2000

Title: "Asbestos fiber type and length in lungs of chrysotile textile and production workers: Fibers longer than 18 μm", Inhalation Toxicology 12 (Suppl 3): 411-418, 2000"

Methods:
- TEM fiber analyses of lung samples of 64 chrysotile textile workers and 43 chrysotile miners & millers
- Counts of fibers ≥18 μm in length & diameter ≥ 0.045 μm.

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Fiber Burden Analyses
Case et al., 2000

Results:
- Geometric mean chrysotile and tremotile concentrations 4 and 12 times higher in miners compared to textile workers.
- Amosite/Crocidolite geometric mean concentrations of 0.024 fibers per µg dry lung in miners and 0.037 textile workers.

Author's Conclusions:
- Fiber length does not explain the lung cancer risk differences between the 2 cohorts
- Amphibole concentrations largely elevated in textile workers who ceased employment before1940.

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Fiber Burden Analyses
Case et al., 2000

Comments and Observations:
- Conclusions based on small and likely non-biologically meaningful differences in amosite/crocidolite fiber concentrations.
- Total amphibole concentrations were actually much higher in miners. Tremolite 12X higher.
- Mesothelioma risk among textile workers is not consistent with a important role for amphiboles.
- Green et al. (1997) - increased amphibole content in only 1 of 10 lung cancers.
- Case-control analyses - lung cancer risk not different in departments where amphiboles used.

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Charleston Cohort Data
Lung Cancer Case-Control Analyses- Methods

- Case-control analyses in order to address period of highest possible amphibole lung burden based on Case et al. report
- 126 lung cancers and 5 matched controls per case.
- Unconditional logistic regression restricted to cases and controls first employed after 1940
- Conditional regression with an dichotomous indicator variable adjusting for employment before 1940 or 1950.

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Charleston Cohort Data
Lung Cancer Case-Control Analyses- Results

Cumulative Asbestos Exposure fiber/cc-years	Odds Ratio Unconditional model with all cases (n=126)	Odds Ratio Unconditional model for workers employed after 1940 (n=92)
<2.7	1.00	1.00
2.7-27.4	2.17	2.07
27.4-109.5	2.90	3.16
27.4-109.5	6.28	9.37

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Charleston Cohort Data
Lung Cancer Case-Control Analyses- Results

Cumulative Asbestos Exposure fiber/cc-years	Odds Ratio Conditional model with adjustment for employment before 1940 (n=126)	Odds Ratio Conditional model with adjustment for employment before 1950 (n=126)
<2.7	1.00	1.00
2.7-27.4	2.17	2.48
27.4-109.5	2.90	3.24
27.4-109.5	6.28	7.01

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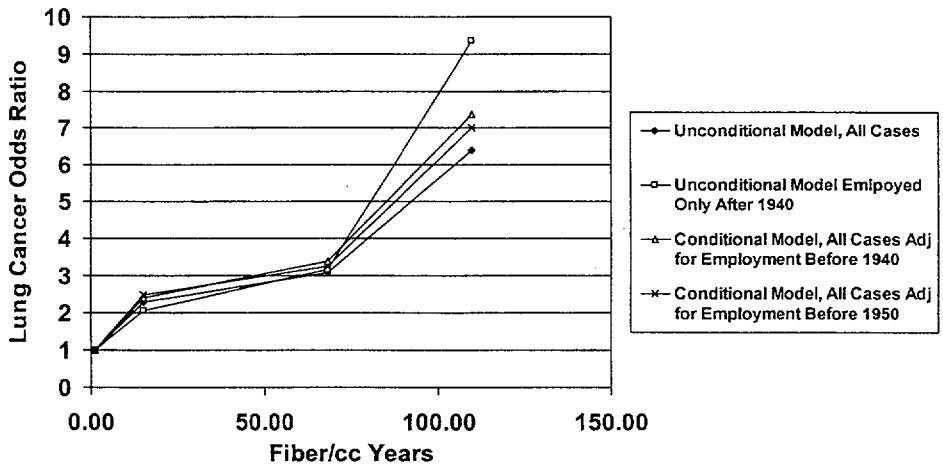
Charleston Lung Cancer
Case-Control Analyses- Comparisons



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Charleston Lung Fibrosis Study
Green et. Al. (1997) - Analyses

- 54 Charleston Workers
- 34 Controls (matched on: age at death, hospital, year of death)
- Fibrosis Score by NIOSH/CAP Method by 3 Pathologists.
  - Severity (0-4)
  - Extend (0-3)
  - Fibrosis Score, Severity x Extent (0-12)
- Mineralogical Analyses of Tissues by TEM (38 workers and 31 controls)
- Cumulative Exposures at Charleston Plant Calculated for Each Worker

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Charleston Lung Fibrosis Study
Green et. Al. (1997) - Conclusions

- Fibrosis scores correlated with estimated lifetime cumulative asbestos exposures and lung fiber burden.
- Median fibrosis scores were higher than controls for all cumulative exposures including the lowest category of 0.1 to 7.1 fiber-years.
- Median fibrosis score for controls = 1.0 and 95% had fibrosis scores 3.0 or less.
- Controls may also have experienced significant asbestos exposures based on their fiber burdens and scores --- risks may be underestimated.

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Charleston Lung Fibrosis Study
Logistic Regression Analyses - Model

- **Case Definition:** Fibrosis Scores >3.0
- **Covariates in Unconditional Logistic Models:**
  - Age (15 year categories)
  - Sex
  - Cumulative Exposure (4 categories)
  - Indicator Variable for any Amosite or Crocidolite in Lung Burden Studies

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Charleston Lung Fibrosis Study
Logistic Regression Analyses - Results

Cumulative Exposure (fiber-yrs)	Fibrosis Odds Ratio All Cases & Controls	Fibrosis Odds Ratio Cases & Controls with Lung Burden Data
<0.1	1.0	1.0
0.1 – 5.0	2.5	3.7
5.1 – 25.0	3.8	13.3
>25.0	24.9	46.2

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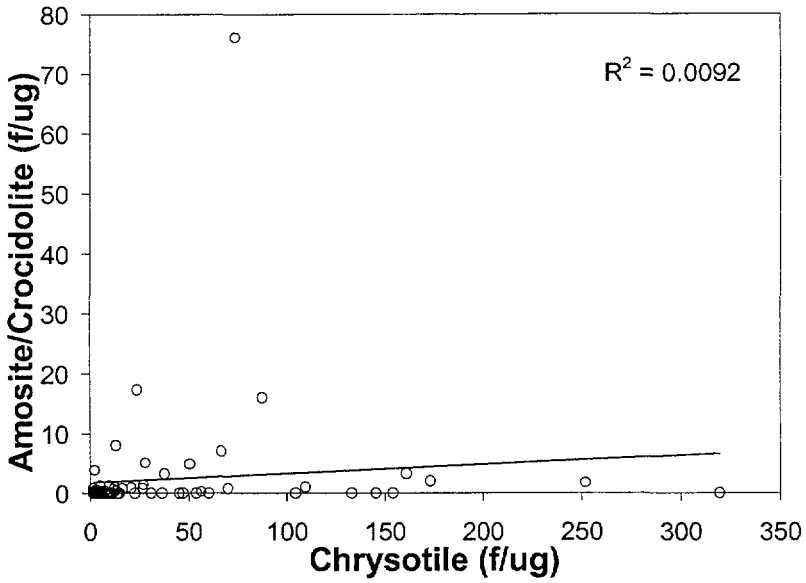
Lung Chrysotile & Amosite/Crocidolite



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Charleston Lung Fibrosis Study

Logistic Regression Analyses - Results

Cumulative Exposure (fiber-yrs)	Fibrosis Odds Ratio Cases & Controls with Lung Burden Data	Fibrosis Odds Ratio Cases & Controls with Lung Burden Data – Adjusted for Any Amosite or Crocidolite
<0.1	1.0	1.0
0.1 – 5.0	3.7	4.3
5.1 – 25.0	13.3	13.3
>25.0	46.2	43.2

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Charleston Lung Fibrosis Study
Logistic Regression Analyses - Conclusions

- The presence of amosite/crocidolite does not significantly change the chrysotile dose response for lung cancer or pulmonary fibrosis.
- Conclusions of Case et al. not supported by their data nor new analyses of Charleston data.
- The OSHA lung cancer risk estimates are consistent with those generated by the Charleston study.
- Chrysotile should not be controlled differently than other asbestos types.

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RADIOLOGICAL CHANGES AS MARKERS OF ENVIRONMENTAL EXPOSURE AND ENVIRONMENTAL RISK OF LUNG CANCER AND MESOTHELIOMA

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Introduction

That certain mineral fibers can cause disease has been known since the early 20th century, when the first cases of asbestosis were described. In the 1940ies the risk of lung cancer was first described and later malignant mesothelioma. It is now well known that mineral fibers can cause diseases and changes in the lung parenchyma and the pleura, which are the main targets since the fibers are inhaled, but also in many other parts of the body. The medical studies come mainly from occupational exposures, but environmental exposure is also possible and can pose grave dangers.

There are many hundred different fibers in the mineral world, both naturally occurring and man-made ones. Only a few do, however, occur in amounts and environments that make it possible for humans to be exposed. Those that are known are the ones collectively known as asbestos and a fibrous zeolite called erionite. There might well exist other fibers in various parts of the world that could lead to human disease but has not yet been recognized.

This review will first describe the benign pleural lesions which can be caused by asbestos and discuss whether they can be used as "sentinel signs" of such exposure, and then give a short review of findings and diseases in "endemic areas", i e places in the world where lesions and/or diseases due to environmental exposure to asbestos have been reported. The different asbestos fibers can give different medical findings.

Diseases and radiological findings caused by asbestos and erionite

Benign pleural lesions

The benign radiological findings which occur after exposure to asbestos are of two main types: firstly, these involving the parietal pleura, i. e. the inside of the chest wall, the diaphragm, and the mediastinal surfaces. These are called pleural plaques. Since the lung is not involved, there is only minor or no affection of lung function by these lesions. Secondly, there are those lesions which involve the visceral pleura, i.e. the outer layer of the lung. These lesions often cause affection of the lung function (1,2).

Pleural plaques

The by far most common asbestos-related lesions are the **pleural plaques**. Macroscopically, they are shining white elevations with sharp borders. Microscopically, they consist of fibro-hyaline connective tissue containing very few cells. There are no inflammatory cells within the plaques, but small aggregates can be seen in their periphery, indicating a low-grade inflammation there.

Radiology. Pleural plaques are best seen in the flanks of the lungs in a frontal view. This is because they are most evident when the X-rays hit them tangentially. If they are thick enough, they can be visible even if not viewed tangentially. When they are calcified, they are much easier to recognize. Diaphragmal plaques can be visible as button-like elevations. The costovertebral sinuses are unaffected. A slow progression over the years is a very typical characteristic (3).

Plaques are always more widespread and numerous at autopsy than at the chest roentgenogram. Only 10 to 15 per cent are seen with conventional radiography (4). If less strict criteria are used at radiology, a few more true plaques will be diagnosed - but the main problem is an overdiagnosis, and in fact half or more of all the diagnosed plaques do not exist in reality. The ILO system is not useful here: the smallest "plaques" diagnosed there (less than 5 mm thick) is very unspecific (5). Computed tomography will demonstrate more plaques but is not suitable for studies on large population groups. In fact, the number of more plaques seen are limited, and plaques on the diaphragm are often missed (6).

It has to be realized that radiological criteria for plaques differ very much between various readers. In any study concerning the occurrence of plaques the criteria used for diagnosing them should be clearly stated. If not very strict criteria are used, a considerable overdiagnosis is unavoidable. This is one possible explanation behind the different opinions about the importance of plaques.

In the general population in a society where there are no "endemic plaques", 80-90 per cent of strictly defined pleural plaques are due to occupational exposure to asbestos (7,8). However, they can be found also in persons with only low-level or sporadic exposure.

There are many normal intrathoracic and extrathoracic structures that can lead to X-ray findings which may be mistaken for pleural plaques. Here are some of the more common:

Fat pads are common, especially in overweight persons. Typically, they are even thickenings along the flanks which start apically and can be followed sometimes down to the costodiaphragmal junction. However, they can also be irregular, and plaques can at times be situated on the fat (9). CT scan can show the fat density (9,10).

Intrathoracic muscles can also cause regular and bilateral findings. *Extrathoracic muscles*, especially the anterior serratus muscle, can also sometimes be a problem. These shadows can be followed outside the thoracic cage, and are regular and "saw-shaped".

"Companion shadows" are soft tissue shadows along the ribs, and are often seen apically but are also common in the flanks further down, and can be very difficult to discriminate from early pleural plaques.

Tuberculous infection and haemorrhagic exudations after trauma can lead to calcifications, usually unilateral, but typically these are situated in the visceral pleura.

Rib fractures, when healed, can appear very much like plaques. Since fractures are often multiple and, especially in alcoholics, bilateral, careful study of the films is necessary. Each rib should be normal and the contours without any defects for a diagnosis of pleural plaques to be made, unless other changes typical of pleural plaques are present.

Other pneumoconioses. In silicosis, pleural calcification can occur but is rare. Talcosis can be very similar clinically and roentgenologically to asbestosis, but it is probably the asbestos found in almost all types of talc that causes the pulmonary and pleural changes (11).

Dose-response. The relation between dose and response for pleural plaques is much weaker than that for parenchymal asbestosis. A good correlation between pleural plaques and asbestos fibers in the lung has been shown by many researchers (12-16). The mean of asbestos fibers or bodies in persons with plaques is as a rule higher than in the normal population, but there is a fairly large variation and a number of persons with plaques will have values little or no different from the general population (15,16). In other words, plaques are associated with a wide range of asbestos burdens which overlaps with that of the control population.

Latency time. Plaques are more related to time after exposure than to the dose. Very few plaques will be seen earlier than 15 years after the first exposure to asbestos, and most will appear only after 30 years. In areas where the population is exposed from birth the first pleural changes will appear after age 30 and the incidence then increases with age. Thus, occurrence of plaques is dependent on cumulative exposure and time since first exposure (17). Many plaques are not seen until long after exposure has ceased. Once seen, they will slowly grow larger over the years, and with time many will calcify (3).

Occurrence of pleural plaques

Plaques are a common occurrence in most countries, reflecting the extensive use of asbestos some decades ago. In industrialized countries in the cities, 2 to 4 per cent of all males above age 40 are usually carriers of plaques; the prevalence is lower in females and in the countryside (12).

Clinical importance of pleural plaques

Plaques are in themselves harmless. They may be regarded as an objective sign of previous asbestos inhalation, and it is this exposure that is of possible importance for the future health. In the literature, it is sometimes recommended that persons with plaques should be followed. However, since they are a fairly common finding, regular investigations of such persons would be costly, and this cost has to be weighed against the potential gains.

Apart from being a sign of asbestos inhalation, plaques are also an indication that sufficient time has elapsed since the first exposure to increase the risk of malignancy from the asbestos exposure. In many occupational cohorts, the incidence of bronchial carcinoma is twice or more as high in those with pleural plaques as in those without but with similar exposure (8,13,14). Persons with plaques also have a risk of developing mesothelioma (8). However, as will be described later, the risk of mesothelioma (and possibly also lung cancer) is related also to the type of asbestos which has caused the plaques: thus, for example, there is a much higher risk to develop mesothelioma if the plaques have been caused by crocidolite exposure than if they had been casused by anthophyllite exposure.

Theoretically, wide-spread calcified plaques might restrict the movements of the chest wall and thereby restrict the lung function. In fact, persons with pleural plaques have as a group a somewhat lowered lung function, but whether this is due to the effect on the chest wall or an associated slight pulmonary fibrosis is unclear.

VISCERAL PLEURAL LESIONS

Typical for the visceral pleural lesions is that the visceral pleura, i e the pleura which covers the lung, is involved. Invariably, this leads to an affection of the lung parenchyma as well, with an affection of the lung function. The so-called diffuse pleural thickening always blurs more or less diffusely with the

parenchyma, and there are always more or less developed "fibrous strands" or "crow´s feet" which reach into the lung parenchyma; and most often there is a blunted costophrenic angle. A peripheral atelectasis of the lung parenchyma can occur; this has been termed "rounded atelectasis" (1,2).

Exudative pleurisy. This can occur suddenly in asbestos-exposed persons. It can be of any magnitude, but can amount to up to two liters. Despite this, the patients are often free of symptoms, and the condition can be a surprise finding at X-ray. The exudate usually persists for some months and can recur after drainage; however, within a year the exudate is usually resolved. Recurrences can occur, either on the same or on the other side. Residually, a diffuse thickening of the pleura or a rounded sinus may be observed, but often the exudate will disappear without trace. Any middle-aged or elderly man with acute or subacute pleurisy should be suspected of having been exposed to asbestos. The diagnosis of asbestos pleurisy is at present based on the history of exposure and the absence of another etiology (18).

Blunting of the costophrenic angle in asbestos-exposed persons is a common finding, but is very unspecific, and a large number of persons who have never been exposed to asbestos can show the same.

Crows´feet are fibrotic strands reaching into the lung from a "shrinkage center" in the visceral pleura. CT scan will beautifully show these lesions, which can reach deep into the lung.

Rounded atelectasis. Although rounded atelectasis was originally described in association with pleural effusions and after therapeutic pneumothorax, there is no doubt that asbestos is the principal cause today. However, any effusion, no matter what the cause, can result in a rounded atelectasis.

The classic mechanism of rounded atelectasis is that described by Hanke (19): within a pleural effusion a part of the lung becomes atelectatic and adheres to another part of the lung. When the exudate is resorbed, the adhesions remain, and when the adjacent parts of the lung expand, some bronchi will be folded, and thus part of the lung cannot refill with air - it has become "trapped". Another mechanism is that a fibrotic changes involving the peripheral part of the lung contracts, forcing part of the lung to become atelectatic.

Occurrence of visceral pleural lesions
The visceral pleural lesions are much less common than are plaques. There are no good studies on their prevalence, probably mainly due to the fact that they are only rarely recognized to be due to asbestos. In most cases they are diagnosed as remnants of unspecific pleurisy.

Importance of visceral pleural lesions
The visceral pleural lesions are associated with a usually quite considerable lowering of lung function (20). Visceral pleural lesions usually also imply a fairly heavy exposure to asbestos, with a risk of other asbestos-related diseases.

Specificity of benign pleural lesions
Strictly defined pleural plaques are practically pathognomonic for asbestos exposure. The visceral types of pleural lesions are more unspecific and may be found with many other types of pleuritis (21).

For the purpose of "sentinel radiologic findings" only pleural plaques are feasible, even if a cohort with a large number of unspecific pleural lesions of the visceral type should alert the epidemiologist. To my knowledge, this has not been described in the literature, however.

It is important to realize the "shortcomings" of pleural plaques in this regard: the long latency time of 30 years or more; the strict definitions that are necessary to avoid overdiagnosis; and the fact that plaques are not rare in an industrialized society.

ASBESTOSIS

Asbestosis, or pulmonary fibrosis can occur with exposure to all types of asbestos. The lung becomes fibrotic and stiff and gas exchange dramatically decreases. It is a dose-related disease, and a fairly high exposure is necessary to cause the clinical manifestation which is shortness of breath. Once the process has started, it continues to worsen. Asbestosis is rare with environmental exposure but can occur after many years of slight exposure.

MALIGNANT TUMORS

The malignant diseases due to asbestos are mainly **lung cancer** and **malignant mesothelioma**. A number of other tumors in the body has been claimed to be increased in asbestos workers but the scientific proof varies and they can be disregarded in a review like this one.

Lung cancer is mainly a disease caused by smoking. However, exposure to asbestos will increase the risk in a dose-related manner. Most data point to a multiplicative effect for smoking an asbestos. In a non-smoker, the risk of developing a lung cancer is very small, and even if this risk is doubled due to asbestos exposure, the risk will remain low. In other words, most "asbestos lung cancers" are also "smoker´s cancers". It is also easily understood that lung cancer is a difficult disease to use as a marker of low dose exposure to mineral fibers, since the main numbers of this disease are caused by smoking which might vary much in the population.

Malignant mesothelioma, however, has no correlation to smoking. Apart from a very small portion which is believed to be the "basal level" of the disease and the very rare cases that are due to other known causes (for instance radiation), all cases can be considered to be due to exposure to asbestos (or erionite). The tumor arises in the pleura and grows slowly there, compressing the lung and in later stages invading the ribs and causing the death of the patient often within a year of diagnosis. Rare cases occur, however, with many years of survival. No curative treatment exists, though some cytostatics seem to have some effect on the tumor. The disease is dose-related but even a slight exposure can be enough. Like pleural plaques, the latency time is usually more than 30 years. Rarely, the disease starts in the peritoneum.

Thus, two findings – pleural plaques and malignant mesothelioma – are useful as "sentinel" diseases, indicating that asbestos (or erionite) exposure has occurred in the cohort.

Mineral fibers of medical interest

The main types of asbestos are those consisting of straight fibers (amphiboles), of which the most important are crocidolite ("blue asbestos"), amosite ("brown asbestos"), tremolite, and anthophyllite, and those with curly fibers, of which there is only one important type, namely chrysotile ("white asbestos"). These fibers all differ in their diameters and lengths and also in their ability to resist breakdown in biological tissues. Chrysotile is by far the most widely used. It also has the fastest clearance from the body. Most diseases seem to be mainly associated with the amphiboles (22). Environmental exposures are reported only for the amphiboles, probably due to the fact that chrysotile breaks down to a much larger extent.

Crocidolite is the most dangerous of the asbestos fibers and is not mined any more. It has certain abilities, such as a high resistance to acids, that made it a very useful industrial substance. *Amosite* is also nowadays rarely used. *Tremolite* has been mined only to small extent but is a common contaminant of chrysotile, talc and many other ores, such as nickel and iron, all over the world. In addition, it is a

common mineral, occurring in outcrops in many places of the world. *Anthophyllite* has been mined in Finland and Japan, but it has today no industrial use.

Erionite, finally, is not a very common mineral. It was formed under certain conditions in volcanic areas of the world and contaminates other zeolite formations there.

Local deposits of fibrous minerals

In many areas of the world, asbestos fibers occur in the soil, as remnants of broken down rocks. Farmers working with the soil are exposed to the fibers, and in many places the locally occurring asbestos has been used for white-washing of houses, construction of fireplaces or sauna stones (23-25). As a result there are areas of the world where pleural plaques are endemic. Such "endemic pleural plaques" were first described from Finland and since then many other areas have been reported (Table I).

The older age groups can show calcified plaques in 50 per cent or more radiographically and even more at autopsy (up to 100 per cent in persons above age 50) though usually the incidence is more modest. Where the fibers occur in the soil, farmers are exposed and then the plaques are more common among males. Where the mineral fibers are used for white-washing of houses, the women also have a high incidence of plaques.

One of the best described countries is Turkey, where there are not only villages with exposure to asbestos but also some where a non-asbestos fibrous mineral has been found to cause endemic pleural changes. This fiber is erionite, a fibrous zeolite, which was formed during volcanic activity and occurs locally in some few villages, the best known of which is called Karain. The erionite occurs in roads, fields, and building stones. Apart from the pleural changes, these villages also have an extremely high incidence of malignant mesothelioma. In fact, this dreadful disease is the main cause of death there (48).

Endemic plaques are of interest also in other countries, since many persons born in these places and living there in their childhood and youth now have moved to other places, taking with them not only the plaques but also the risk of mesothelioma and lung cancer.

What should be done about asbestos and erionite occurring locally?

As mentioned, Turkey is the best investigated country for these local findings, but as can be seen from table II, many other countries are also affected. Most probably, the problem is much more wide-spread and many other countries in the world probably have similar problems, only the risk has not been identified as yet. This is probably most likely in the developing countries, but many of the risks (for instance, in Corsica and Greece) have been identified only within the last one or two decades, so it is quite possible that new findings can be made also in industrialized countries.

Once the problem has been identified, the most important next step is to inform those affected of the risk and which habits should be avoided. For instance, white-washing of houses should be abandoned or rather other substances should be used. Good results will be achieved by this method alone, as shown in a recent paper from Turkey where there are indications that the incidence of mesothelioma is going down (49), and from Metsovo. In the erionite case in Turkey, where the problem is not any particular use of the substance but rather that it occurs in the ground, the only solution is to move the village.

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TABLE I. Local deposits of mineral fibres (asbestos or erionite), incidence of plaques, and of malignant mesothelioma

Country or area	Type of fiber	Population or activity	Incidence of plaques	Mesothelioma risk	Reference
	Tremolite				
Austria		Vineyard & field workers	Increased	Not increased	26,27
Bulgaria		Tobacco growers	Increased	Not increased	28
Corsica		General population	Increased	High	29,30
Cyprus		General population	Increased	High	31
Greece		White-washing houses	High	High	32-35
New Caledonia		White-washing houses	High	High	36,37
Turkey		White-washing houses Farmers	High	High	25,38,39
	Amosite				
South Africa		Population around mine	High	High	40
	Crocidolite				
South Africa		Population around mine	High	High	40
Rep. of China		General population	High	High	41
	Anthophyllite				
Finland		Population around mine	High	Not increased	42-44
Japan		Population around mine	High	Not increased	45
	Unknown				
Czechoslovakia		Farmers	High	Unknown	46
USSR		General population	Increased	Unknown	47
	Erionite				
Turkey		Villagers	High	Extremely high	39,48

Carcinogenicity of fibrous tremolite in workplace and general environments

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Summary of paper to be presented at EPA Asbestos Health Effects Conference, Oakland, California on May 24, 2001

Background

The McGill programme of epidemiological research in Quebec chrysotile miners and millers, initiated in 1965, was conducted largely in the belief that exposure in that industry was to chrysotile only. While investigating the uneven distribution of pleural changes among workers in the various mines and mills, Gibbs was probably the first to suggest, in 1979, that the explanation might lie with minerals other than chrysotile. Some years earlier, however, when Pooley and Rowlands *et al.* examined by electron microscopy lung tissue taken at autopsy from former miners and millers, chrysotile and tremolite fibres had been seen in surprisingly similar concentrations. These observations raised the question of the extent to which the fibrogenic and carcinogenic consequences of exposure were attributable to tremolite, chrysotile or both.

The fact that tremolite fibres may penetrate the airways more deeply than chrysotile, and are certainly more persistent in lung tissue, has little epidemiological significance unless there is also evidence of their greater pathogenicity. That this is so was shown in the 1980s by a McGill study of a small cohort of 406 vermiculite miners and millers in Libby, Montana where, among 165 deaths, there was a substantial excess of lung cancer, NMRD, and four deaths ascribed to mesothelioma. At the same time, a radiographic survey of current and retired Libby mine workers found a close correlation between prevalence of small opacities and cumulative exposure (f/ml.y). A further observation of potential importance, made by Sébastien *et al.*, was that the concentration of asbestos bodies in sputum was as good or better a predictor of radiographic changes as cumulative exposure estimated from environmental measurements. Mortality and radiographic studies undertaken by NIOSH in parallel, but on slightly different study groups, resulted in very similar findings to our own. It was uncertain, however, whether the fibres to which these workers were exposed, although classified mineralogically as in the tremolite series, were necessarily the same biologically as those found in association with Quebec chrysotile.

Tremolite contamination of chrysotile

In the cohort of some 11,000 male Quebec miners and millers, almost 10,000 of whom were alive in 1930, 38 cases of mesothelioma were identified among over 8000 deaths before 1993. Of these, five were from a small asbestos products factory where commercial amphiboles were also used and the remaining 33 were in miners and millers: 25 from mines in the Thetford Mines region and eight from the large mine at Asbestos. There was reason to believe that the proportion of tremolite in the chrysotile was some three times higher in the former than the latter, but it was not then known whether the distribution of tremolite was responsible for this apparent difference in risk.

To resolve the question, an analysis was made of deaths from mesothelioma (21), cancers of the lung (262), larynx (15), stomach (99), and colon and rectum (76) in men employed by the largest company in Thetford Mines, with closely matched referents. Risks were estimated by logistic regression for these five cancers in two groups of mines – five mines located centrally and ten mines located peripherally; tremolite contamination had been demonstrated to be some three times higher in the former than in the latter. Odds ratios for work in the central mines were found to be raised substantially and significantly for mesothelioma and lung cancer, but not for the gastric, intestinal or laryngeal cancers. In the peripheral mines, or indeed in Asbestos, Quebec, there was little or no evidence of increased risk for any of these five cancers. The hypothesis that, because of the difference in distribution of fibrous tremolite, cancer risks in the central area would be greater than in the periphery, was thus confirmed, implying that this might well be due to their far greater biopersistence.

Biopersistence and the amphibole hypothesis

Use of a single commercial term, asbestos, to cover at least five fibrous silicate minerals, each with quite different physical, chemical and biological properties, has done much to inhibit proper consideration of their individual health effects. Whereas it has been consistently evident from cohort studies of Quebec miners and millers since the early 1970s that chrysotile rarely caused mesothelioma and, except at very high levels of exposure, was not a major cause of lung cancer, comparable information on miners and millers of crocidolite and amosite was not available until 20 years later. Meanwhile, thanks to the fact that occupational exposures were usually to chrysotile amphibole mixtures, the field became confused and subject to considerable controversy about what has become known as the amphibole hypothesis.

The differences in opinion lie primarily in the interpretation of the epidemiological data. Cohorts exposed only to commercial chrysotile experienced far fewer deaths from mesothelioma and generally lower SMRs from lung cancer than those in which exposure had been to the commercial amphiboles or to products to which the amphiboles had been added. In summary, of 11,538 deaths in chrysotile cohorts, 44

were from mesothelioma and 267 were lung cancers in excess – proportional mortalities of 3.8 and 23.1 per thousand respectively. In amphibole-related cohorts, of 19,622 deaths, 590 deaths were from mesothelioma and 1042 lung cancers in excess – proportional mortalities of 30.1 and 53.1 per thousand. Although these differences in risk are large and consistent, others have drawn quite different conclusions.

At the heart of the controversy lies a fundamentally differing view of the importance of biopersistence in carcinogenesis. It is generally agreed that amphibole fibres are far more durable in lung tissue than chrysotile, and many see this as the explanation of what is observed in human studies. Within the same conceptual framework the results of controlled lung burden studies fit well, as do the current views of experimentalists on the role of biopersistence. On the other hand, those critical of the amphibole hypothesis see differences in fibre persistence as a reason for rejecting the results of lung burden studies, continuing instead to put more store on fibre dimensions.

Results now in press of a national case-referent study in the UK of 115 recent cases of mesothelioma in men aged ≤52 years at death, with lung fibre analysis in 69, do not support the view of the critics. Odds ratios were significantly raised in only 8 of 37 industrial occupations – carpenters, plumbers, electricians, insulators, unskilled construction workers and men employed in ship/boat building or the manufacture of cement and other asbestos products. Amphibole fibres were found in all but 6 of the 69 cases, in concentrations related linearly and highly significantly to adjusted odds ratios. The estimated proportion of cases attributable to amphiboles was 84%, including 7% to tremolite, often considered a marker for chrysotile.

Libby update

So far as the amphibole fibre, tremolite, is concerned, evidence for a high level of carcinogenicity, equivalent indeed to that of crocidolite, is strongly supported by a recent update of the Libby vermiculite mining cohort. Of the 406 men originally identified, 165 had died by July 1, 1983; the 241 survivors have now all been followed until January 1, 1999, among which there had been 120 deaths, all with certified cause. A comparison of SMRs in the two periods, against mortality rates, for US white males, is shown in Table 1. The results in the two periods are very similar, except that the total number of mesothelioma deaths (excluding three possible cases) had now reached 12 (PMR = 4.2%), and external causes (i.e. accidental death) are no longer in excess. Risks in relation to duration and intensity of exposure are now being analysed.

Table 1. Libby Cohort of vermiculite miners exposed to fibrous tremolite (n = 406)

	Deaths to July 1983		Deaths since July 1983*	
	n	*SMR*	*n*	*SMR*
Respiratory cancers	23	2.45	21	2.22
All other cancers	20	1.09	19	1.21
NMRD	21	2.55	30	3.35
Circulatory diseases	65	0.87	36	0.96
External	23	1.87	3	0.99
All causes	165	1.17	1.20	1.34
(incl. mesothelioma)	4 (PMR = 2.4%)		8 (PMR = 6.7%)	

to Jan 1, 1999

Synthesis

Further consideration of the research which has been reviewed suggests reasonable and probably reliable conclusions. Our findings at Libby, supported by the earlier studies of NIOSH, indicate that amphibole fibres in the tremolite series, in the absence of any other asbestos fibre types, are highly fibrogenic and carcinogenic for both lung and pleura. Results from the McGill and NIOSH studies in the 1980s estimated the excess risk of lung cancer to be about 1% per fibre year and of small radiographic opacities (≥1/0), at roughly 0.6% per fibre year. The excess mortality, all causes, in the Libby cohort to date, for whom the mean cumulative exposure is estimated at 145 f/ml.y, was 13.3%. Assuming linearity, and ignoring other possible factors, the estimated risk (all causes) is thus about 0.09% per f/ml.y. These levels of risk are probably sufficient to explain most if not all the adverse effects of exposure to commercial chrysotile.

The validity of all these estimates is put into question, however, by the fact that in both Thetford Mines and Libby, risks were related to duration of employment but not to average intensity of exposure. Having regard for the extremely uneven geological distribution of tremolite deposits in both these locations, it is not surprising that average exposure in terms of f/ml is virtually impossible to estimate. This limitation applies particularly to any attempt at assessing general environmental risks for inhabitants of regions where deposits of fibrous tremolite occur. In these circumstances, the further development and quantification of asbestos bodies in sputum may provide a useful approach.

HEALTH EFFECTS OF NON OCCUPATIONAL EXPOSURE TO ASBESTOS

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NON OCCUPATIONAL CIRCUMSTANCES OF EXPOSURE

- Domestic exposure from ACM
- Environmental exposure pollution
- Environmental exposure
- Environmental non occupational exposure in buildings

DOMESTIC EXPOSURE

- *Newhouse et al (1965), Lieben et al (1967), Milne (1972), Vianna et al (1978,1980), Nicholson (1983), Bianchi et al (1982, 1987), Schneider et al (1996):* **numerous reports of mesothelioma cases in spouses of asbestos workers (cleaning contaminated work-clothes), and in various domestic and neighborhood circumstances (contact with ACM)**
- *Magnani et al (2000*)**: population-based case-control study in three countries (Switzerland, Spain, Italy); 53 cases and 232 controls without known occupational exposure; elevated risk for domestic exposure (OR=4.8); dose-response pattern**
- *Bourdes et al (2000):* **meta-analysis of 8 mesothelioma studies; summary RR for household exposure=8.1 (5.3-12)**

ENVIRONMENTAL FROM INDUSTRIAL POLLUTION

ASBESTOS MINES AND MILLS

South Africa

- *Wagner et al (1960):* some occupational exposure
- *Webster et al (1973):* among 130 known occupational exposure, occurring between 1956 and 1970, 76 lived near a CROCIDOLITE mine
- *Botha et al (1986):* excess of mortality for lung cancer, asbestosis and mesothelioma in CROCIDOLITE mining districts compared with control districts
- *Rees et al (1999):* among 22 mesotheliomas with exclusively environmental exposure, 20 were from the Cape CROCIDOLITE mining area
- *Kielkowski et al (2000):* excess of mesothelioma mortality among white women of the Prieska cohort (CROCIDOLITE mining and milling district)

Australia

- ***Armstrong et al (1984), Gardner and Saracci (1989):*** **among 37 mesotheliomas without known occupational exposure, occurring between 1960 and 1986 in Western Australia, 6 lived near the Wittenoom CROCIDOLITE mine**
- ***Hansen et al (1998):*** **27 mesothelioma cases between 1943 and 1993 in the cohort of former residents of Wittenoom (n=4,659) not employed in the CROCIDOLITE industry.**
  - **incidence similar for men and women**
  - **rate increased with time since first exposure, duration and cumulative exposure**

Quebec

- ***Camus et al (1998):*** **lung cancer and mesothelioma mortality (1970-89) among women living in the vicinity of Asbestos (CHRYSOTILE mining and milling) and Thetford Mines (CHRYSOTILE CONTAMINATED BY TREMOLITE mining and milling).**
  - **no increased lung cancer risk**
  - **7 mesothelioma cases (Thetford Mines , SMR: 990)**
  - **unusually high exposure level estimates:**
    - ***mean ambient levels between 1.2 and 1.4 f/ml during the 40' and the 50'***
    - ***average cumulative lifetime exposure: 25 f/ml/year (5-125)***

Other countries

- **Finland (*Kiviluoto, 1960*), Bulgaria (*Zolov et, 1967*), Japan (*Hiraoka et al, 1998*): high frequency of pleural plaques among people living close to ANTHOPHYLLITE mining and milling facilities**
- **Austria (*Neuberger et al, 1978*): high frequency of pleural plaques among people living close to a ACTINOLITE mine**
- **China (*Luo et al, 1998*): farmers living pollution rural area" compared to a control group in the same province: strong excess of lung cancer (RR=5.7) and mesothelioma (RR=182)**

ENVIRONMENTAL EXPOSURE FROM INDUSTRIAL POLLUTION

FACTORIES

(cement, textile, brakes, shipyards)

The Casale Monferrato Study

(Marconi et al, 1989, Magnani et al, 1991, 1995)

- Small Italian town (40,000 inhabitants in town; 98,000 in the area) in a non industrial region
- Asbestos-cement factory operating in town from 1907 to 1985: mainly CHRYSOTILE, about 10 % of CROCIDOLITE
- 44 mesothelioma cases without known occupational exposure (26 men, 18 women) diagnosed between 1980 and 1989
- 10 % of cases < 50 year old; men/women ratio close to 1
- airborne fibers >5 μm in town (1984): 1 to 11 f/liter

Incidence of mesothelioma in the Casale Monferrato Study (1980 - 1989)

	CM AREA	CM TOWN	SURROUNDING TOWNS	VARESE PROVINCE	ITALY
MEN					
N	26	20	2	18	159
RATE/100,000	4.2	8.2	0.6	1.0	1.8
WOMEN					
N	18	16	2	7	70
RATE/100,000	2.3	5.1	0.7	0.3	0.6

Recent studies

- ***Magnani et al (2000)*: mesothelioma population-based case-control study in three countries (Switzerland, Spain, Italy); 53 cases and 232 controls without known occupational exposure; elevated risk for living within 2 km of asbestos mines, asbestos-cement, asbestos-textile plants, etc.(OR=11.5); dose-response pattern for distance from factories**
- ***Bourdes et al (2000):* meta-analysis of 8 mesothelioma studies; summary RR for neighborhood exposure=7.0 (4.7-11)**

ENVIRONMENTAL EXPOSURE FROM ASBESTOS IN SOIL

Turkey

- ***Baris et al(1978,1979), Dumortier et al (20001)*** **: extremely high incidence of mesothelioma in the Cappadoce region : 108 cases diagnosed between 1970 and 1987 in the village of Karain (600 inhabitants); rate: 800/100,000 (half of the deaths) : ERIONITE**
- ***Yazicioglu et al(1976,1980), Baris et al(1979,1981,1988), Selçuk et al (1992), Metintas et al (1999), Seyigit et al (2000)*** **: extremely high incidence of pleural plaques, asbestosis and mesothelioma in different villages of rural Anatolia and in the Southeast of Turkey; material quarried from the mountains and used for whitewashing floor and walls of houses; mainly TREMOLITE, small amount of CHRYSOTILE**
  - ***mean age : about 50 (25 % < 40); sex ratio close to 1***
  - ***incidence decreasing in regions where use of asbestos-containing soil has ended (from 105 /million in the first studies to 43/million in the 90')***

Greece

- ***Bazas et al (1985), Constantopoulos et al (1985, 1987), Langer et al (1987), Sichletidis et al (1987,1992), Sakellariou et al (1996):*** **the use of a TREMOLITE containing material ("*luto*") for whitewashing houses associated with a high frequency of pleural calcifications ("*Metsovo lung*"), then with mesothelioma in the Northwest part of Greece**

  . ***1980-1984: 3.7 mesothelioma cases per 10,000 person-years***

  . ***1985-1994: 1.4 mesothelioma cases per 10,000 person-years***

  θ ***Luto whitewash used by 92% of the population in the 50', 18% in 1980 and no more used since 1985***

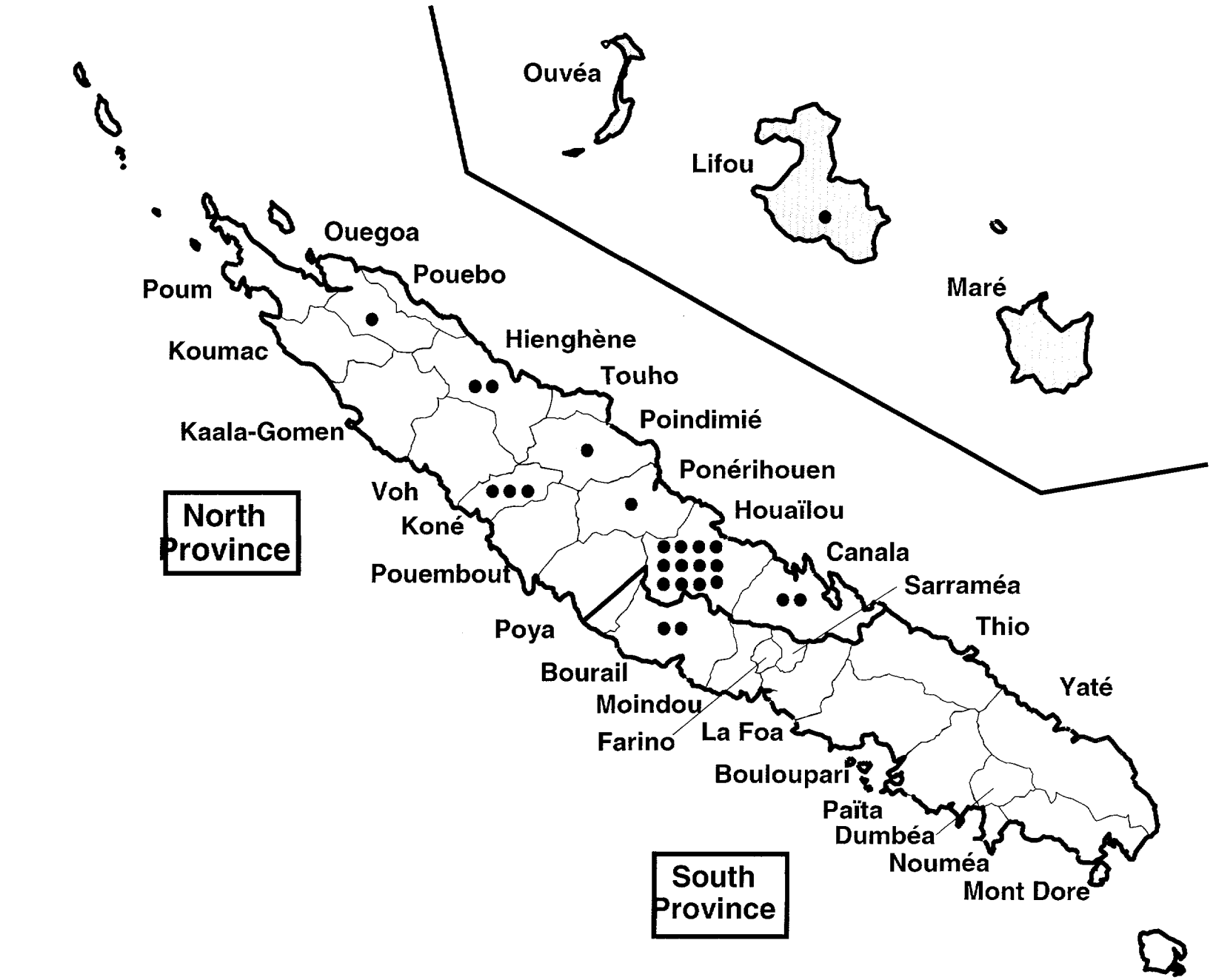
New Caledonia

(Goldberg et al, 1991, 1995; Luce et al, 1994, 2000)

- Identification of a cluster of mesothelioma
- Sex ratio close to one
- Some young cases
- No history of occupational exposure to asbestos for 26 cases among 28
- Mainly Melanesians (23/28)
- Most of the cases in the same rural area

Cluster of MPM cases (1984-1993)

AGE	MEN	WOMEN
30-39	0	3
40-49	2	1
50-59	5	5
60+	6	6
TOTAL		13
	15	


Ouvéa
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Ponérihouen
Voh
Houaïlou
Koné
Canala
Pouembout
Sarraméa
Poya
Thio
Bourail
Yaté
Moindou
La Foa
Farino
Bouloupari
Païta
Dumbéa
Nouméa
Mont Dore
North Province
South Province

Friable rock used as a whitewash ("pö")

Case-control study (1993-1995)

ORs for exposure to pö

	MPM (all: n=15)	LUNG CANCER (Melanesian women: n=30)
Ever exposed	41 (5-325)	4.9 (1.1-21)
Exposed during<20 y	22 (2-221)	1.5 (0.1-27)
Exposed during ≥20 y	65 (8-550)	5.9 (1.2-29)
Age first exp: birth	53 (6.5-427)	4.3 (0.9-144)
Age first exp:≤16 y	20 (1-368)	____
Age first exp:>16 y	____	8.9 (0.5-144)

Other countries

- *McConnochie (1987):* **cluster of mesothelioma associated with environmental exposure from an asbestos mine and house whitewashing in Cyprus; both CHRYSOTILE and TREMOLITE fibers found in whitewash samples and lungs of animals**
- ***Balandraux-Lucchesi et al (1990), Billon-Galland (1988), Rey et al (1993*):excess of pleural plaques and mesothelioma in Northeast Corsica;TREMOLITE fibers in the soil and small amounts of CHRYSOTILE**
- *Paoletti et (2000):* **cluster of mesothelioma in Eastern Sicily in a town where stones from nearby quarries were used in the local building industry; samples from the quarries, the buildings and lung of a mesothelioma case contained TREMOLITE-ACTINOLITE asbestos**

Summary of environmental and biological measurements

COUNTRY	ENVIRONMENT		LUNG (MILLION F/G DRY LUNG)	
	MATERIALS	AIRBORNE SAMPLES	HUMANS	ANIMALS
TURKEY « Erionite-village »	rock: erionite, rare tremolite; roads: same + rare chrysotile; whitewash : erionite, tremolite	street: < 0.01-0.02f/ml; schoolyards: 0.01-0.175 f/ml; indoors: 0.01-1.38f/ml (60-80% erionite, rare tremolite);	erionite: 17, 39 chrysotile : 2, 15 tremolite (1 - 5 % vol)	erionite: 0.13 chrysotile : 4.27
« Asbestos-villages »	whitewash, roads: tremolite	tremolite , chrysotile	tremolite, rare chrysotile	
GREECE	soil: rare tremolite, rare chrysotile; whitewash: tremolite	outside: 0.01-0.02 f/ml indoors: 0.01 et 17.9 f/ml	tremolite , rare chrysotile	
CYPRUS	whitewash, roof dust: chrysotile , tremolite		tremolite: 220, chrysotile: 115	tremolite: 0.02-7, chrysotile: 7.8-78.5
CORSICA		outside (ng/m^3): tremolite : 12 ± 6.6, chrysotile : 15.5 ± 10.9; indoors: tremolite : 59.8 ± 48, chrysotile : 14.3 ± 15.7	tremolite : 1.4-62, chrysotile : 0.3-3.4	52-82 (5% tremolite, 95% chrysotile)
NEW-CALEDONIA	whitewash, rock : tremolite, chrysotile	outside: tremolite (0.025 f/ml), rare chrysotile; indoors: tremolite 78f/ml (sweeping), rare chrysotile	tremolite : 21.9 (0.08-81), chrysotile : 0.13	

CONCLUSIONS

What did we learn from environmental exposure epidemiological studies ?

- Evidence of strong effects of non-occupational exposures: domestic, industrial and natural
- No difference between men and women
- No apparent effect of age at first exposure (latency, risk)
- Fiber type:
  - major role of the amphiboles (crocidolite, tremolite)
  - chrysotile almost always present in lung samples of cancer cases

TIME VARIABLES

	Occupational	Environmental
Age first exposure	Adult	Birth
Years/life	40	All life
Hours/week	40	168
Frequency	Intermittent	Continuous

Key determinants of risk

- Type of fibers
- Intensity of exposure in different circumstances
- Cumulative levels of exposure:
  - time and duration of exposure
  - nature and frequency of daily life activities

What is needed for risk assessment for environmental exposure?

Better data on:

- Fiber characteristics
- Intensity of exposure associated with various exposure circumstances and activities
- Lifetime histories of duration and frequency of exposure in these circumstances and activities

θ Reconstruction of typical exposure situations and lifetime experiences in places where historical situations are still present

2001 Asbestos Health Effects Conference
Oakland, California

Friday, May 25, 2001

8:30 – 8:40 **Welcome and review of agenda**

8:40 – 10:00 **Session 3. Toxicology, Pathology, Mechanisms**

Introduction by Kevin Driscoll, Session Chair, Proctor and Gamble Pharmaceuticals, USA

Cynthia Timblin, University of Vermont, USA
Molecular and cellular mechanisms of asbestos fiber toxicity

Bice Fubini, University of Torino, Italy
The physical and chemical properties of asbestos fibers which contribute to biological activity

10:00 – 10:15 **Break**

10:15 – 12:00 **Session 3. Toxicology, Pathology, Mechanisms (continued)**

Günter Oberdörster, University of Rochester, USA
Fiber characteristics, environmental and host factors as determinants of asbestos activity

Agnes Kane, Brown University, USA
Mechanisms of asbestos carcinogenesis

Discussion: Toxicology, Pathology, Mechanisms

12:00 – 1:00 **Lunch (on your own)**

1:00 – 2:30 **Session 4. Roundtable Discussion of Risk Assessment Methods**

Introduction by Gene McConnell, Session Chair, Toxicology and Pathology Services, USA

Panelists include:
Bruce Case, McGill University, Canada
Julian Peto, Institute of Cancer Research, England
Kevin Driscoll, Proctor and Gamble Pharmaceuticals, USA
Mort Lippmann, New York University, USA
Kenny Crump, ICF Kaiser Engineers, USA
Leslie Stayner, National Institute for Occupational Safety and Health, USA
Aparna Kopikar, Environmental Protection Agency, USA
↳ (revising existing Health Assessment (roughly 3 yr. process).

2:30 – 2:45 **Break**

2:45 – 4:00 **Session 4: Roundtable Discussion of Risk Assessment Methods (continued)**

Facilitated Discussion of Risk Assessment Methods

4:00 – 4:30 **Closing Remarks, Peter Grevatt,** Environmental Protection Agency, USA

Molecular and Cellular Mechanisms of Asbestos Fiber Toxicity

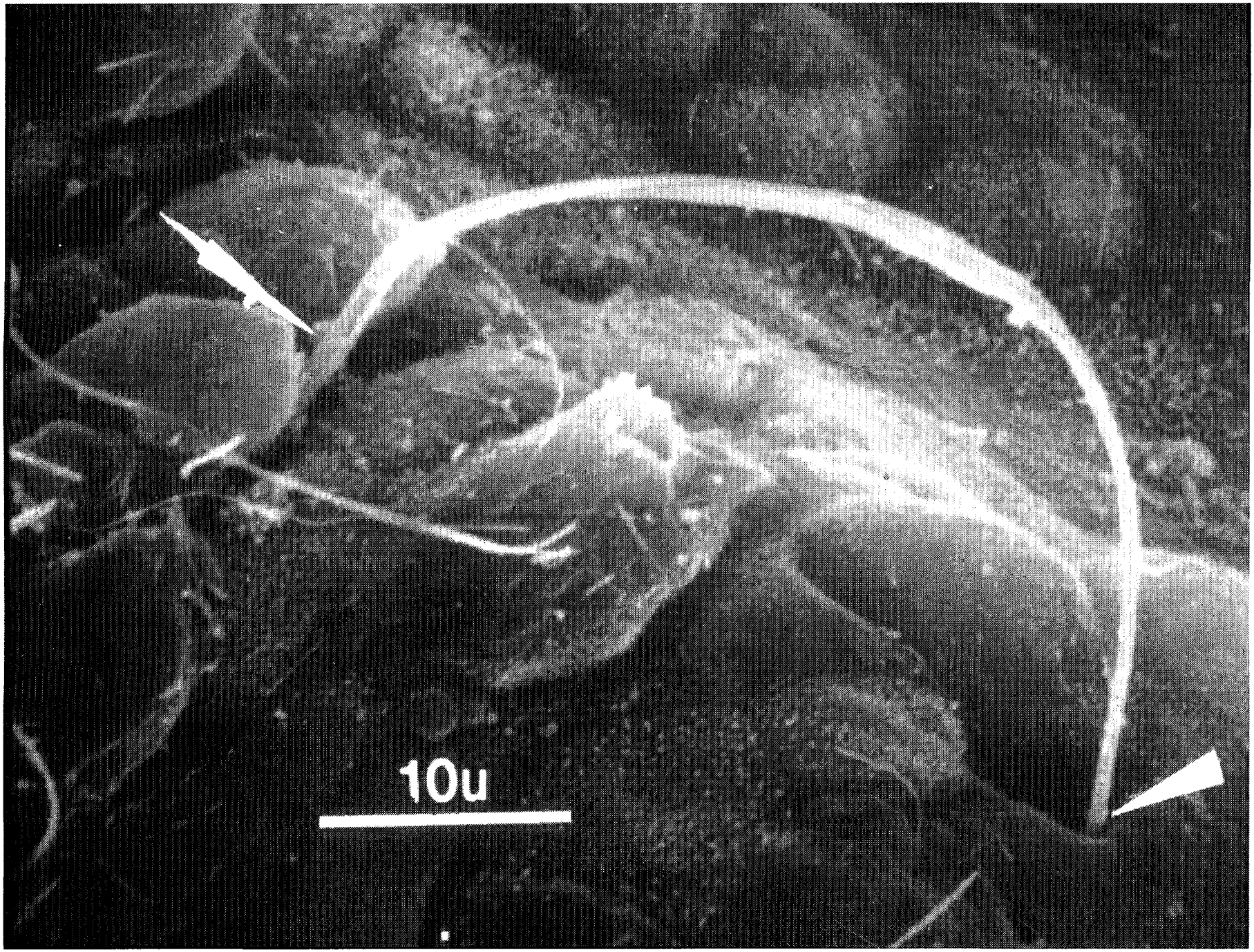
Cynthia Timblin, Ph.D.
University of Vermont

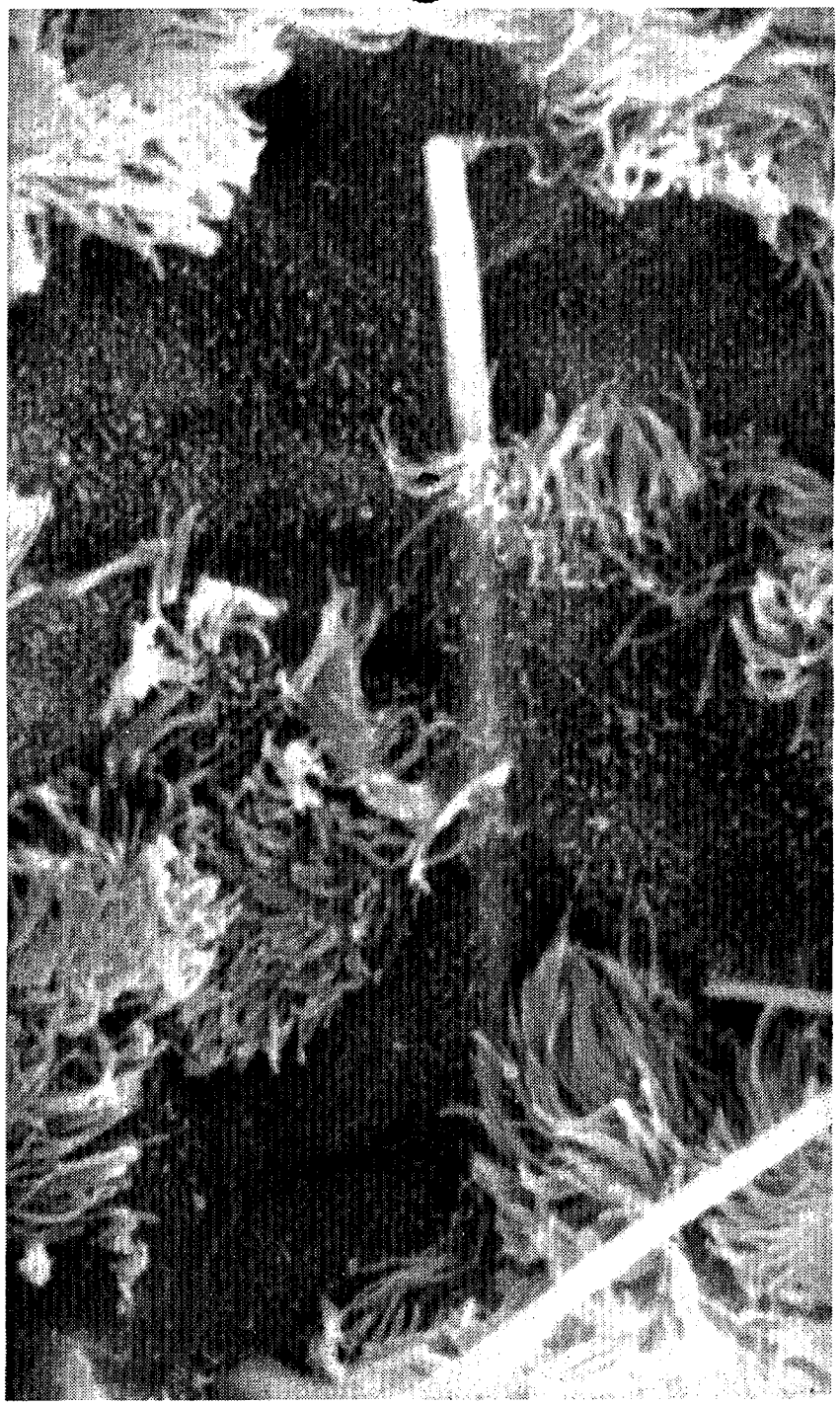
Cellular and Molecular Mechanisms of Asbestos Fiber Toxicity

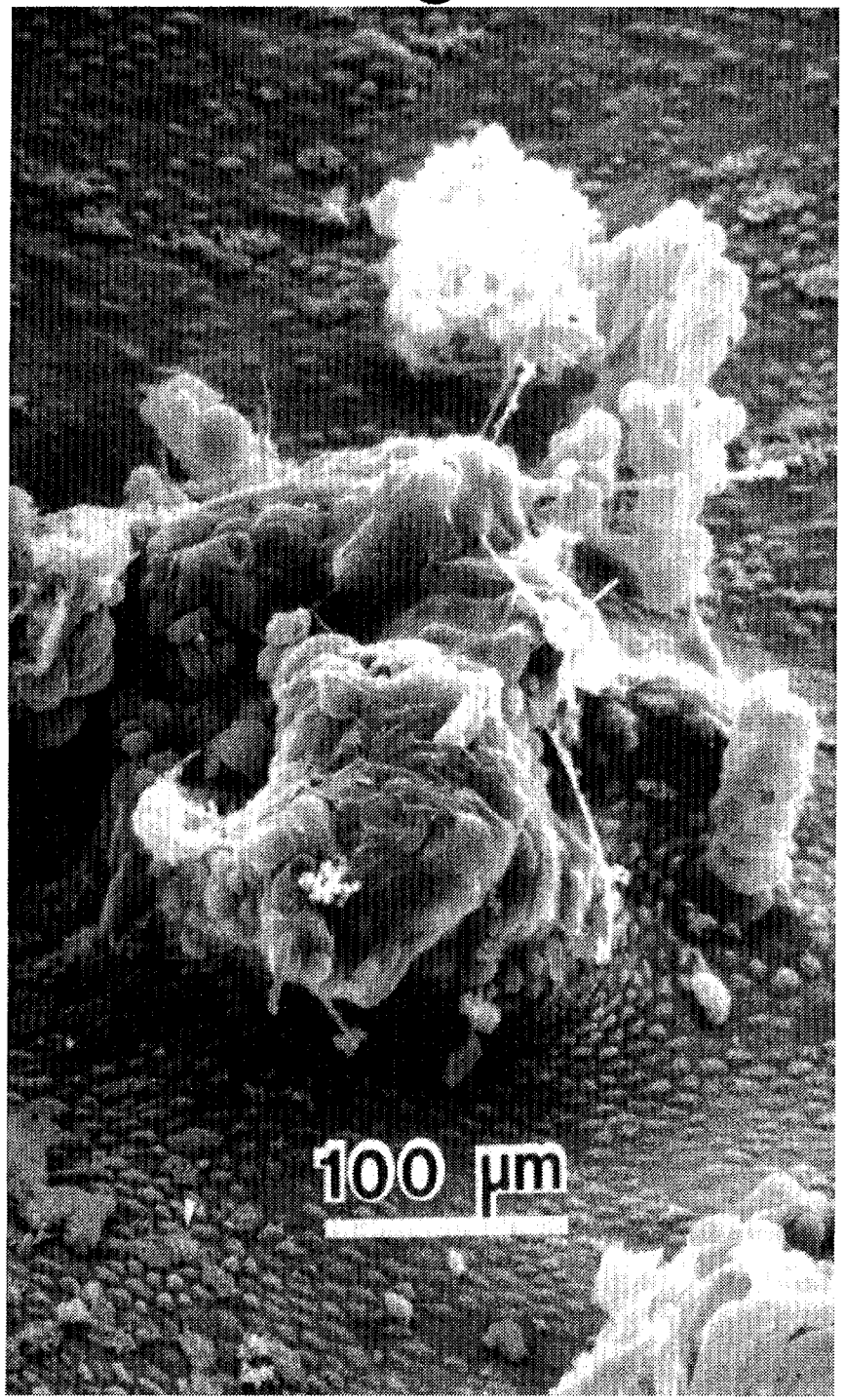
- Interaction of asbestos fibers with cells of the respiratory tract
  - chemical and physical properties of fibers
  - iron-catalyzed reactions that generate reactive oxygen species (ROS)
- Sequence of cellular events after inhalation of asbestos fibers
  - inflammatory response
  - production of cytokines/chemokines/growth factors
  - cell injury and proliferation

Mechanisms cont.

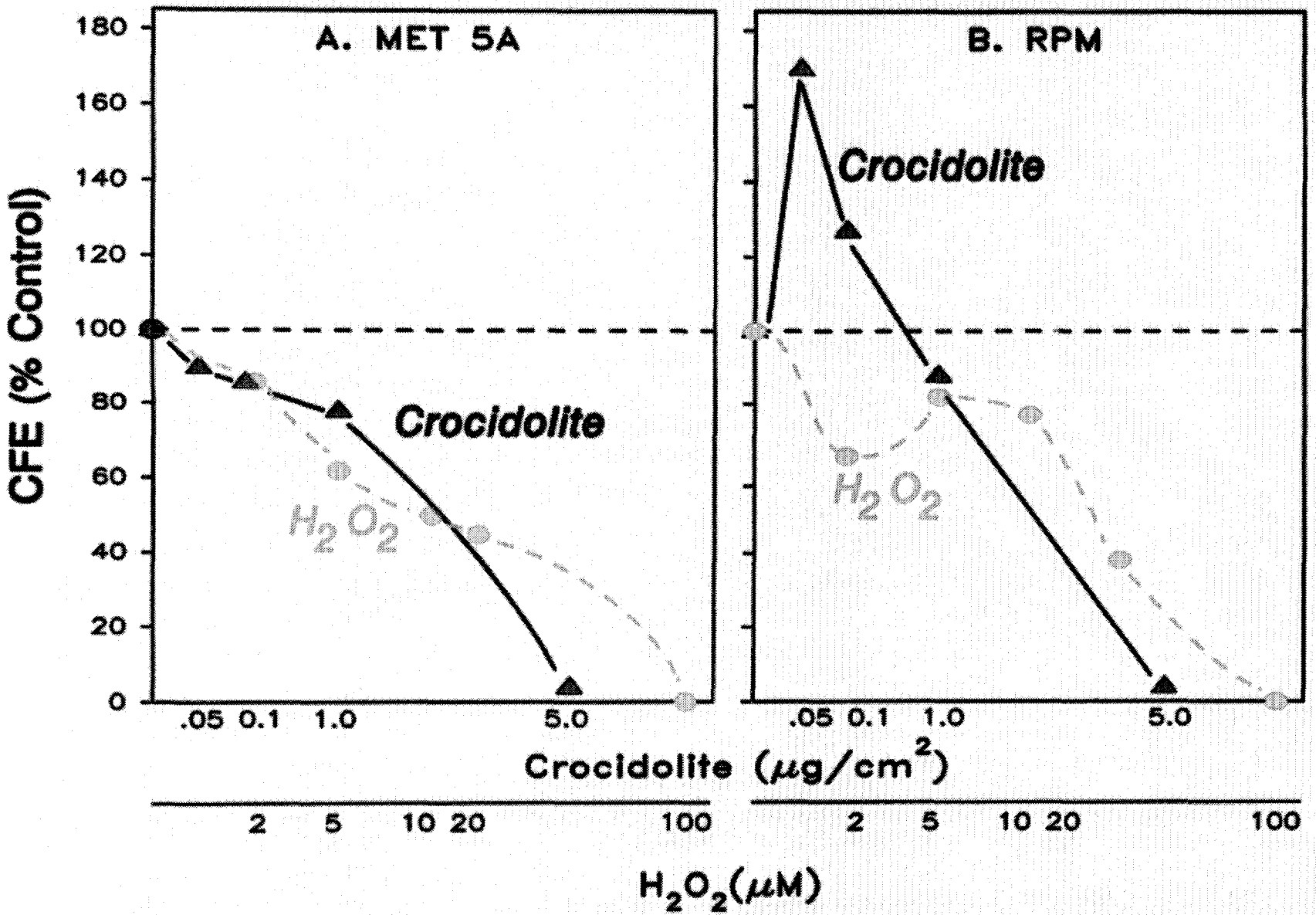
- Sequence of cell signaling events stimulated by asbestos fibers
  - signal transduction pathways [e.g., Mitogen Activated Protein Kinase (MAPK) pathway]
  - activation of transcription factors [e.g., Activator Protein-1 (AP-1)]
  - alterations in gene expression
  - cell injury, survival, proliferation, transformation

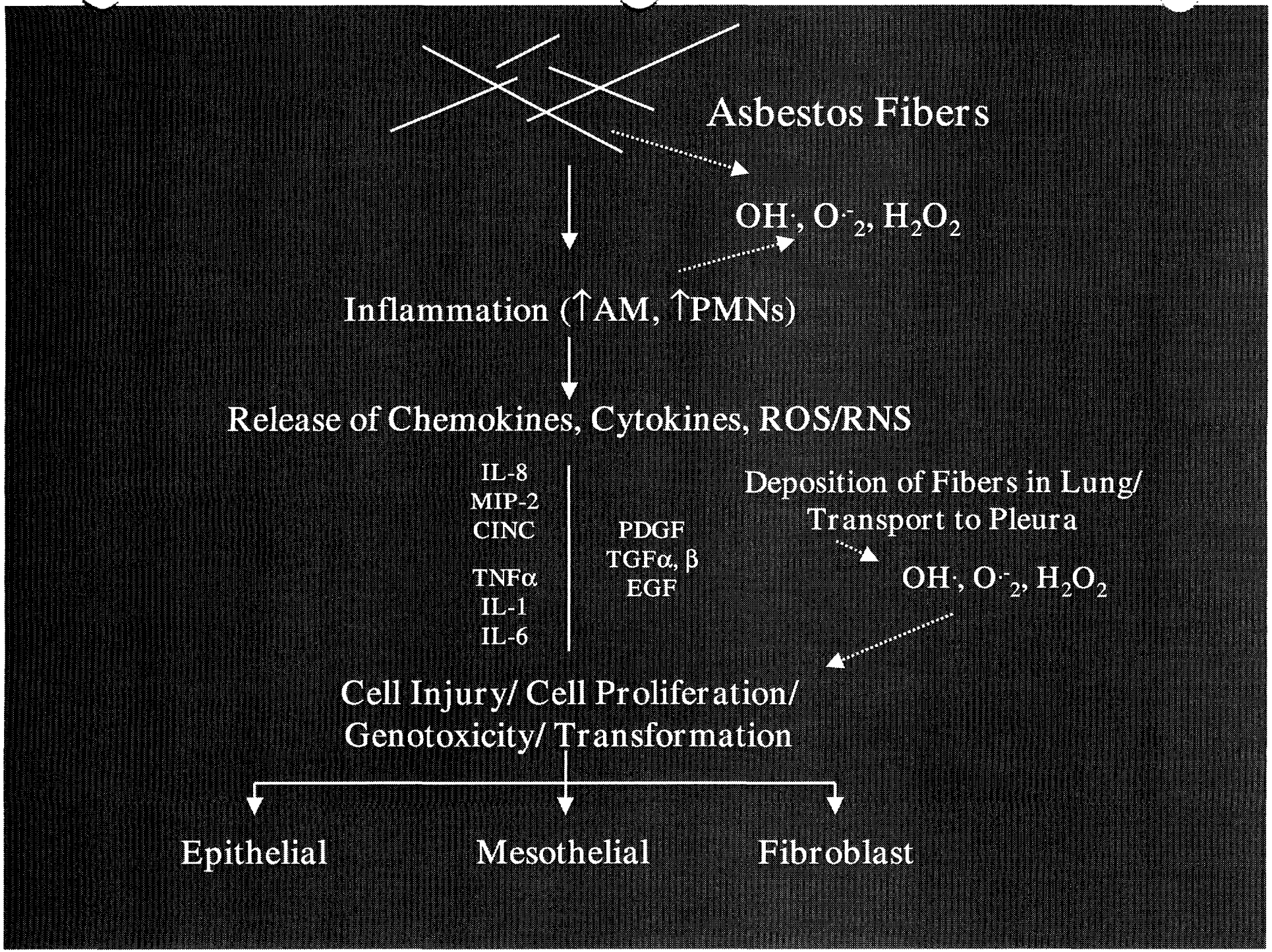

10u

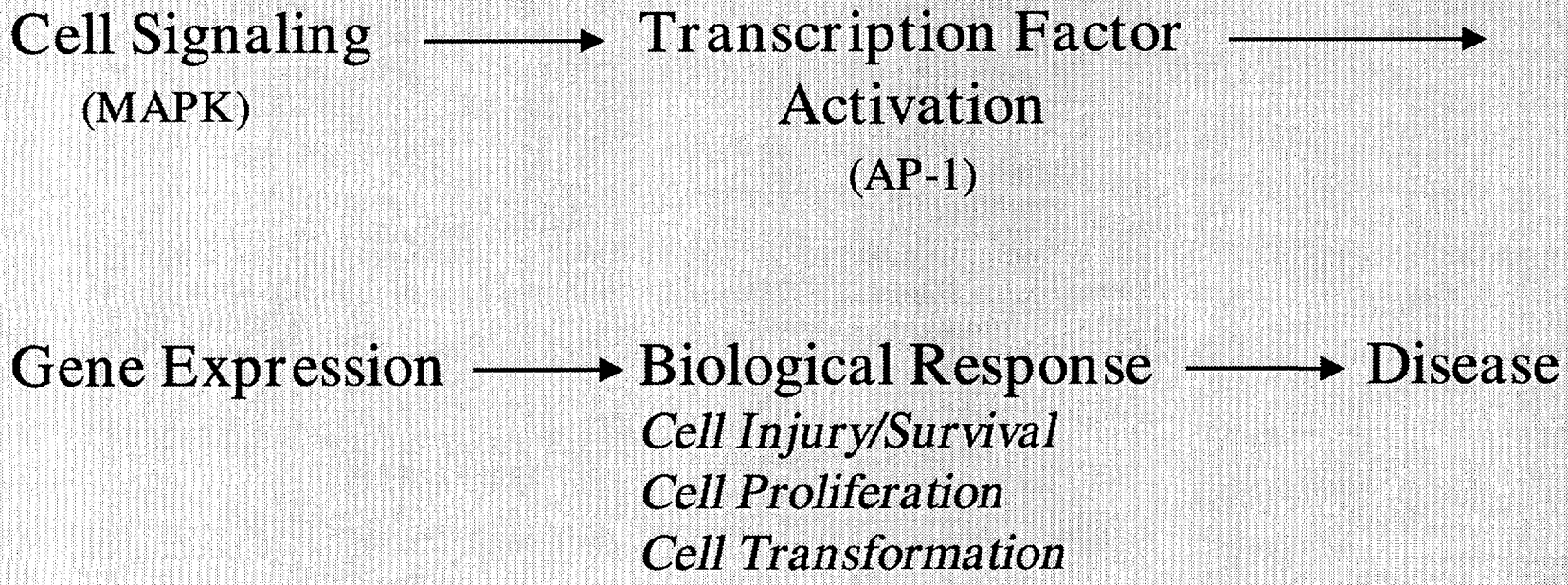



100 µm

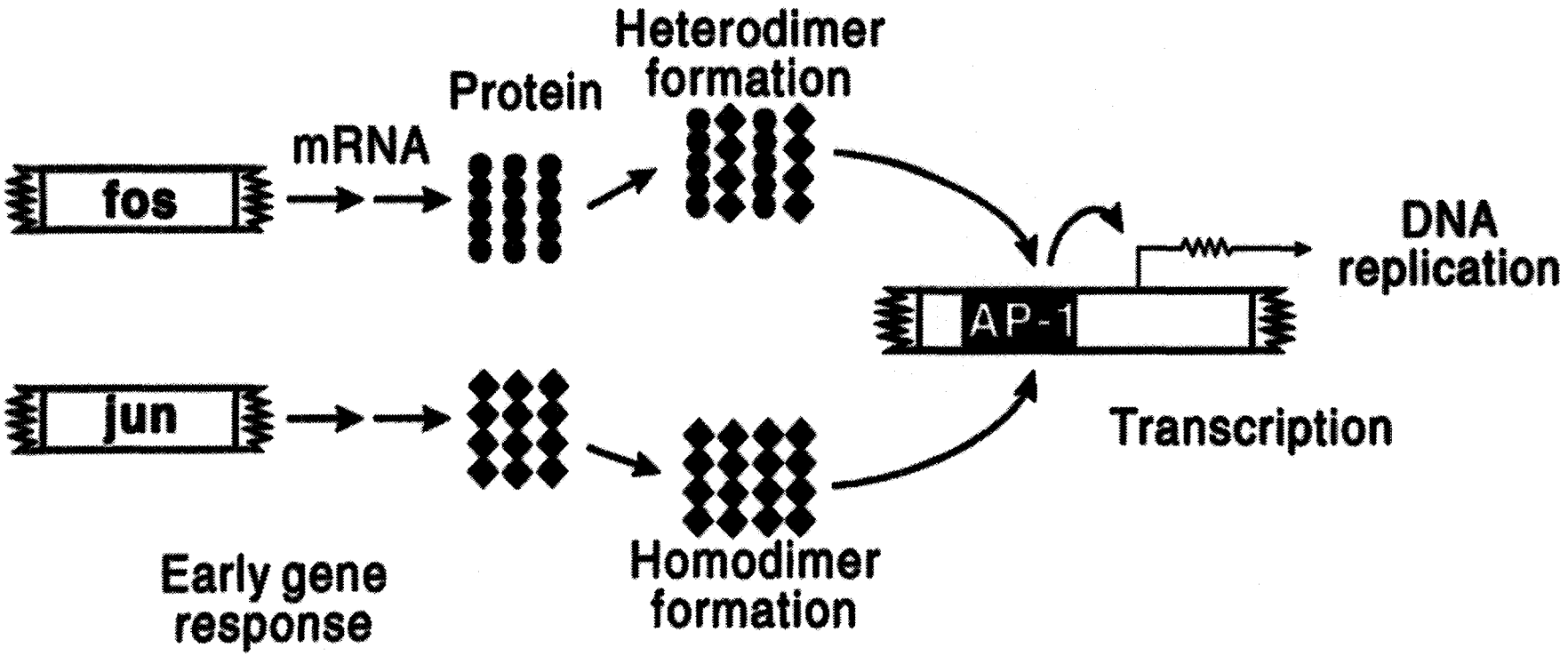
COLONY FORMING ABILITY OF HUMAN MET 5A CELLS AND RAT PLEURAL MESOTHELIAL (RPM) CELLS FOLLOWING EXPOSURE TO ASBESTOS



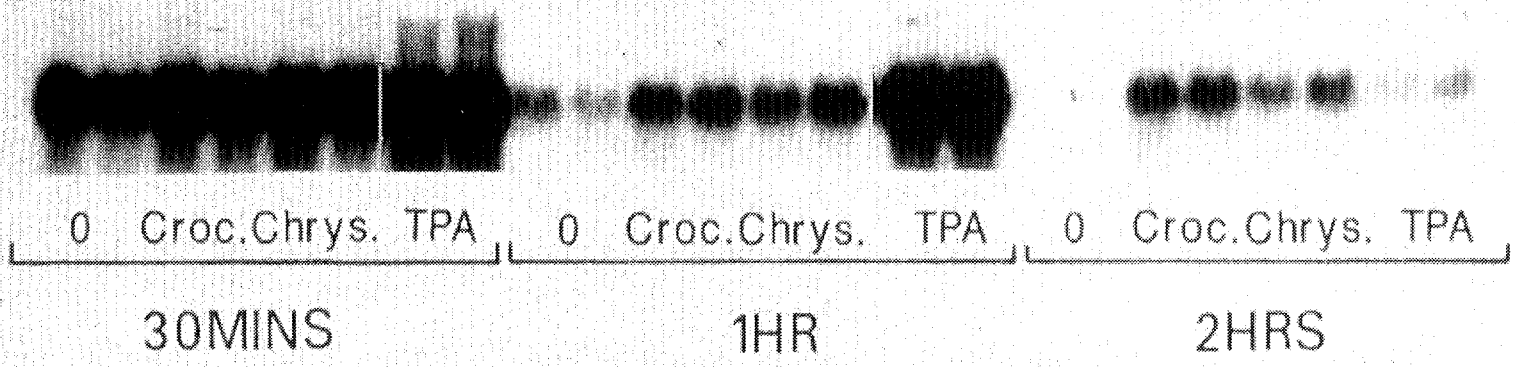

Asbestos Fibers
OH·, O·-2, H2O2
Inflammation (↑AM, ↑PMNs)
Release of Chemokines, Cytokines, ROS/RNS
IL-8
MIP-2
CINC
TNFα
IL-1
IL-6
PDGF
TGFα, β
EGF
Deposition of Fibers in Lung/
Transport to Pleura
OH·, O·-2, H2O2
Cell Injury/ Cell Proliferation/
Genotoxicity/ Transformation
Epithelial
Mesothelial
Fibroblast

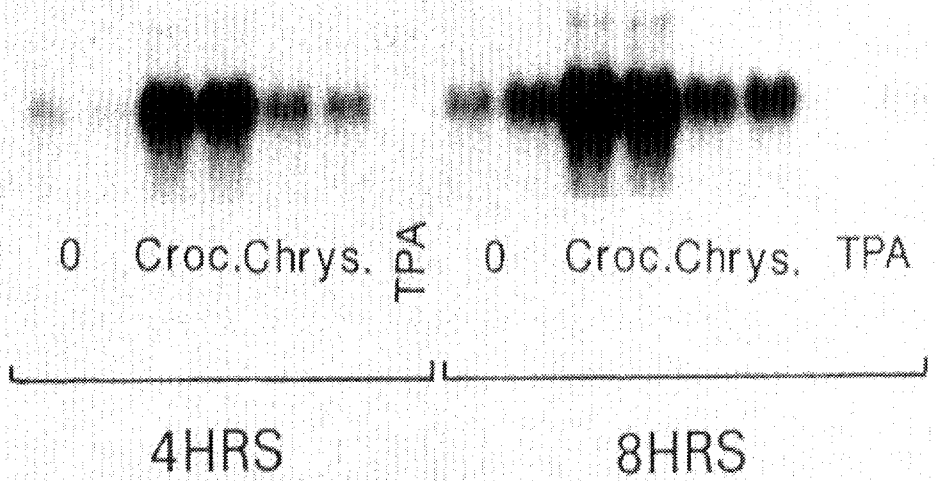

Cell Signaling
(MAPK)
Transcription Factor
Activation
(AP-1)
Gene Expression
Biological Response
Cell Injury/Survival
Cell Proliferation
Cell Transformation
Disease

MECHANISMS OF ACTION OF c-fos/c-jun

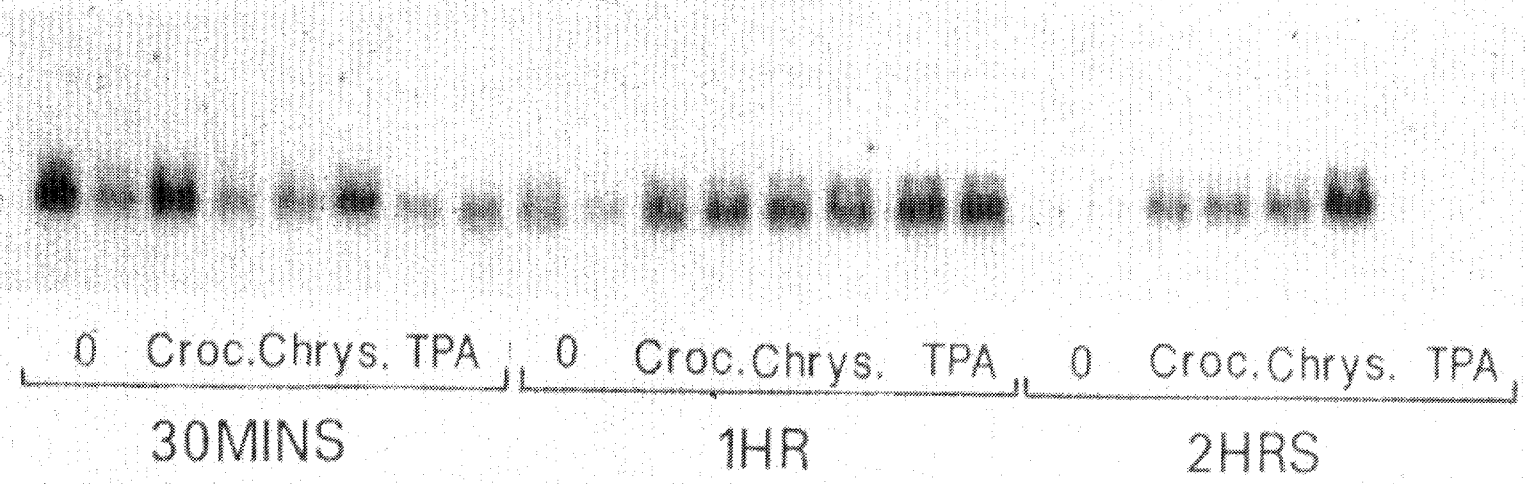


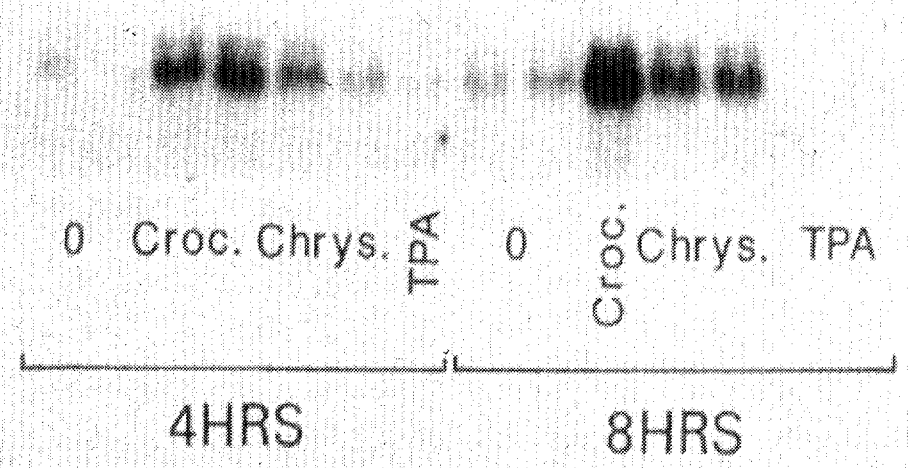
Steady-state mRNA Levels of c-fos in Rat Pleural Mesothelial Cells (RPM)

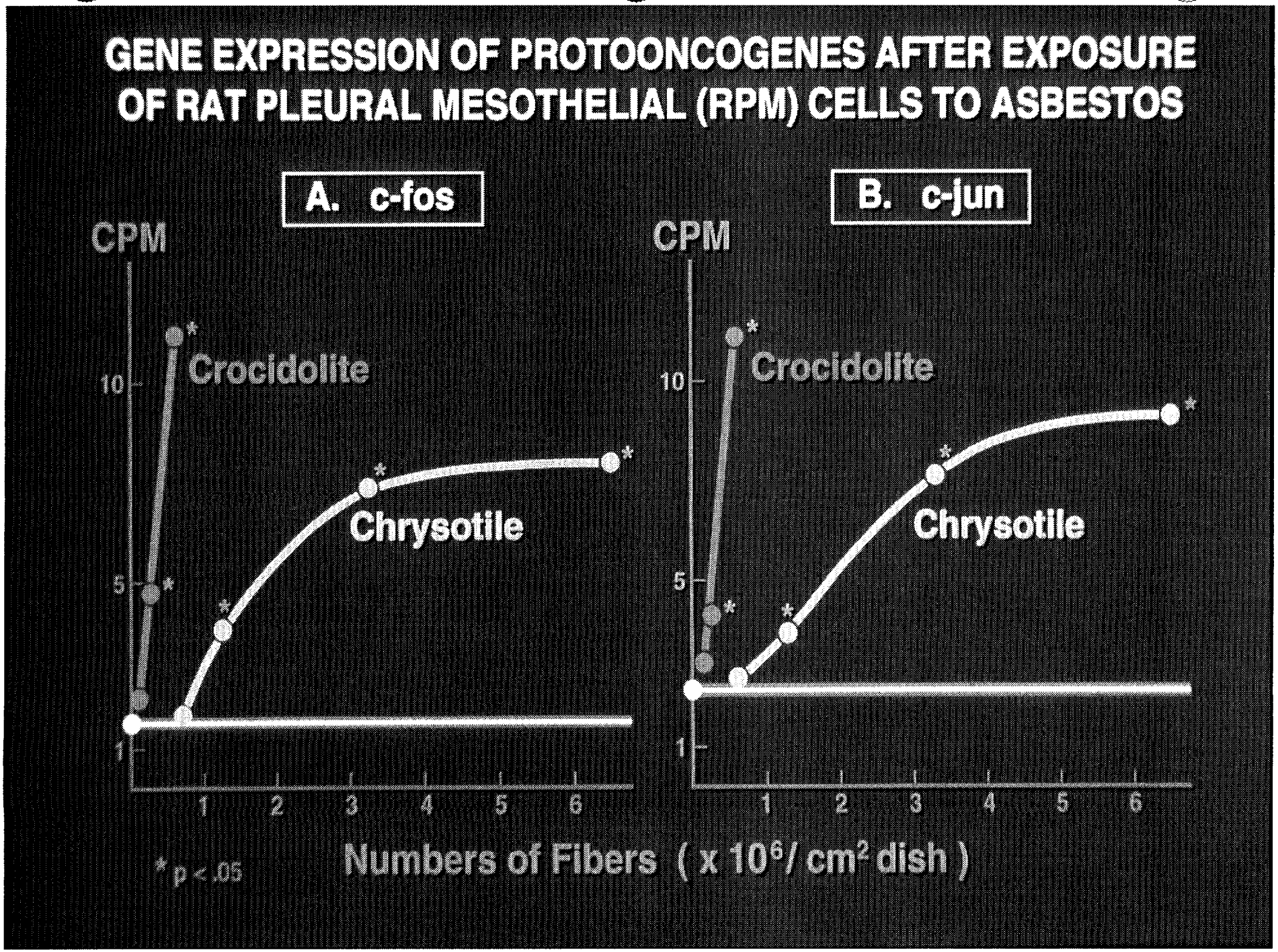




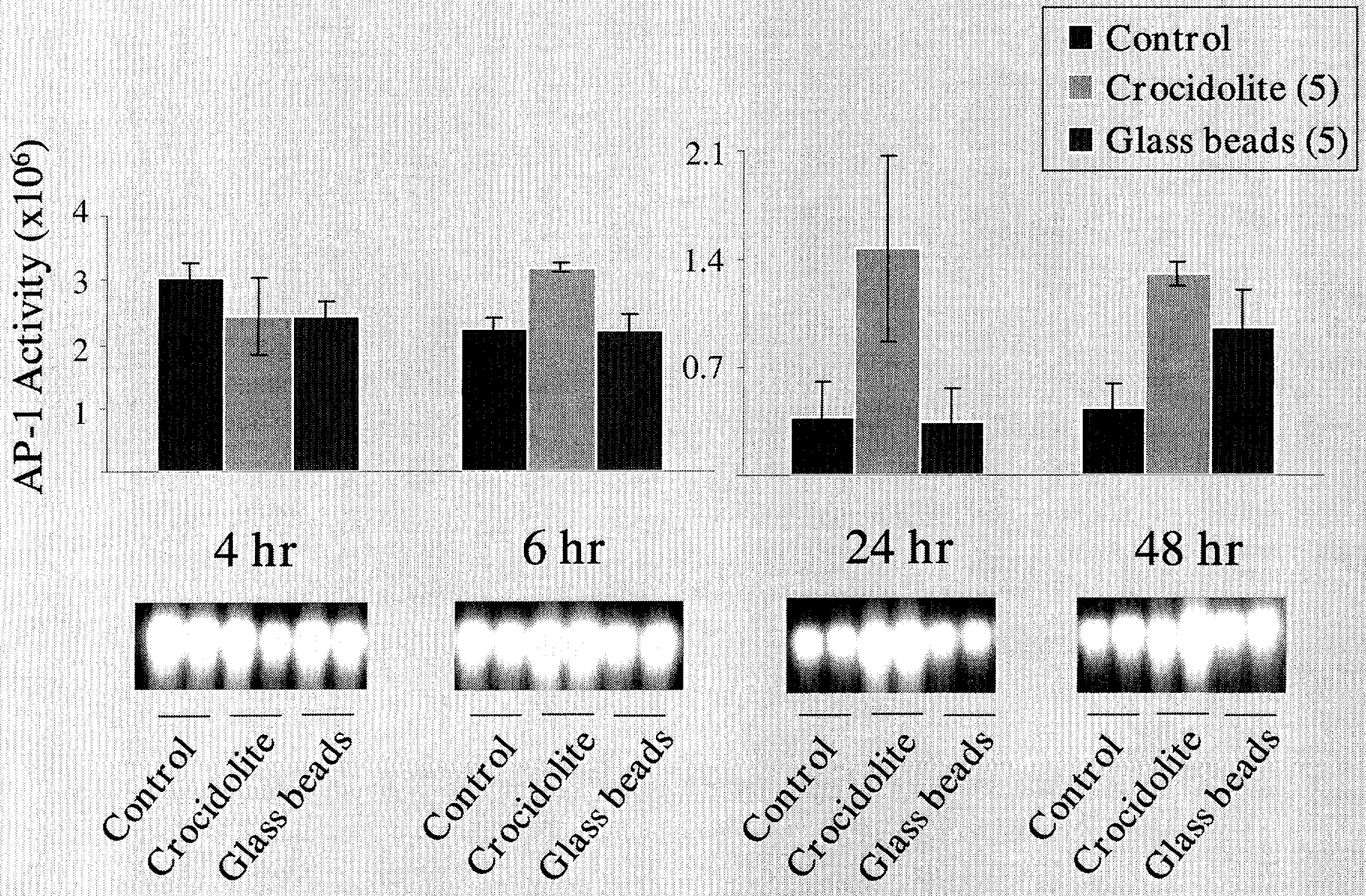
Steady-state mRNA Levels of c-jun in Rat Pleural Mesothelial Cells (RPM)

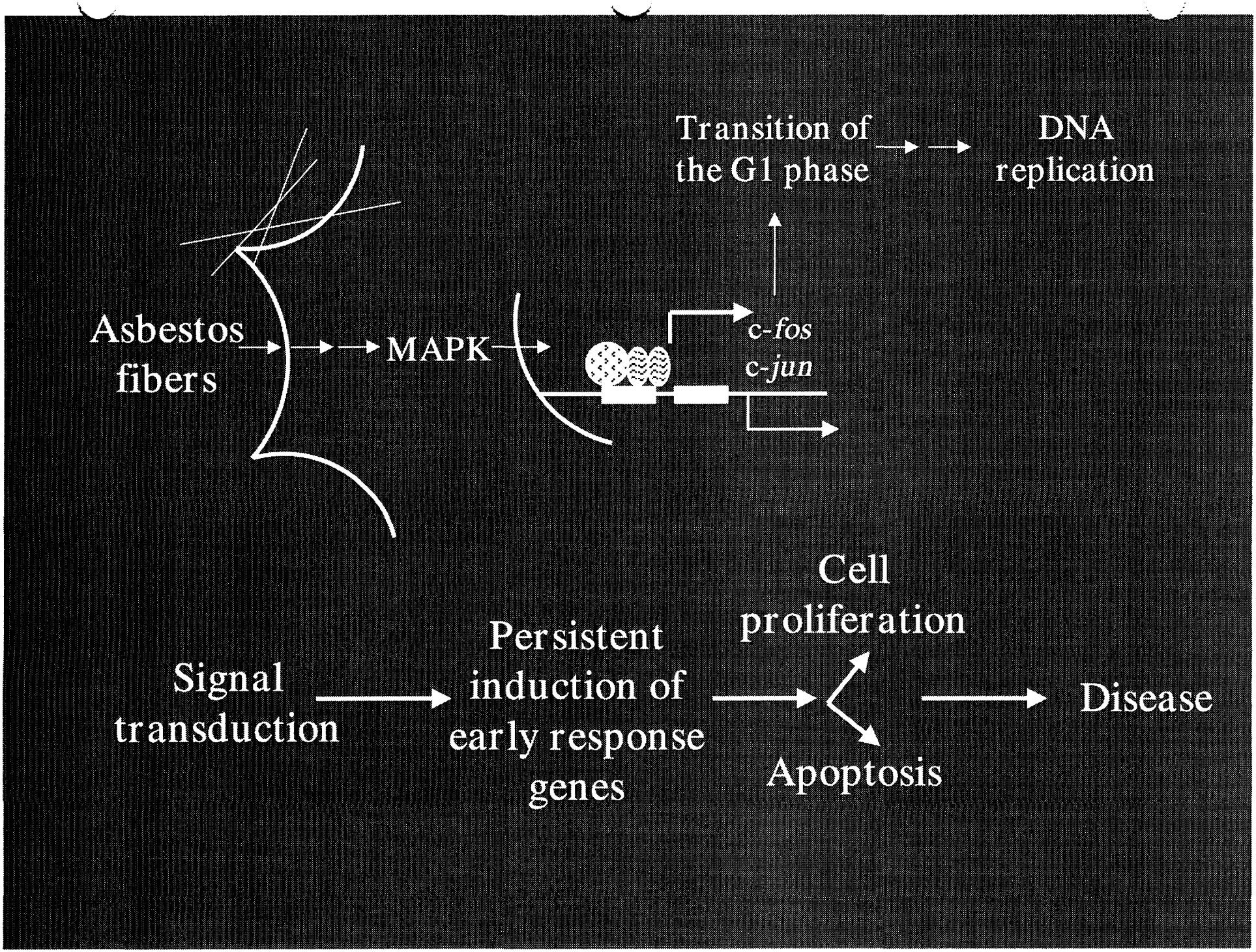





GENE EXPRESSION OF PROTOONCOGENES AFTER EXPOSURE OF RAT PLEURAL MESOTHELIAL (RPM) CELLS TO ASBESTOS
A. c-fos
B. c-jun
CPM
Crocidolite
Chrysotile
10
5
1
1 2 3 4 5 6
* p < .05
Numbers of Fibers (x 10⁶/ cm² dish)

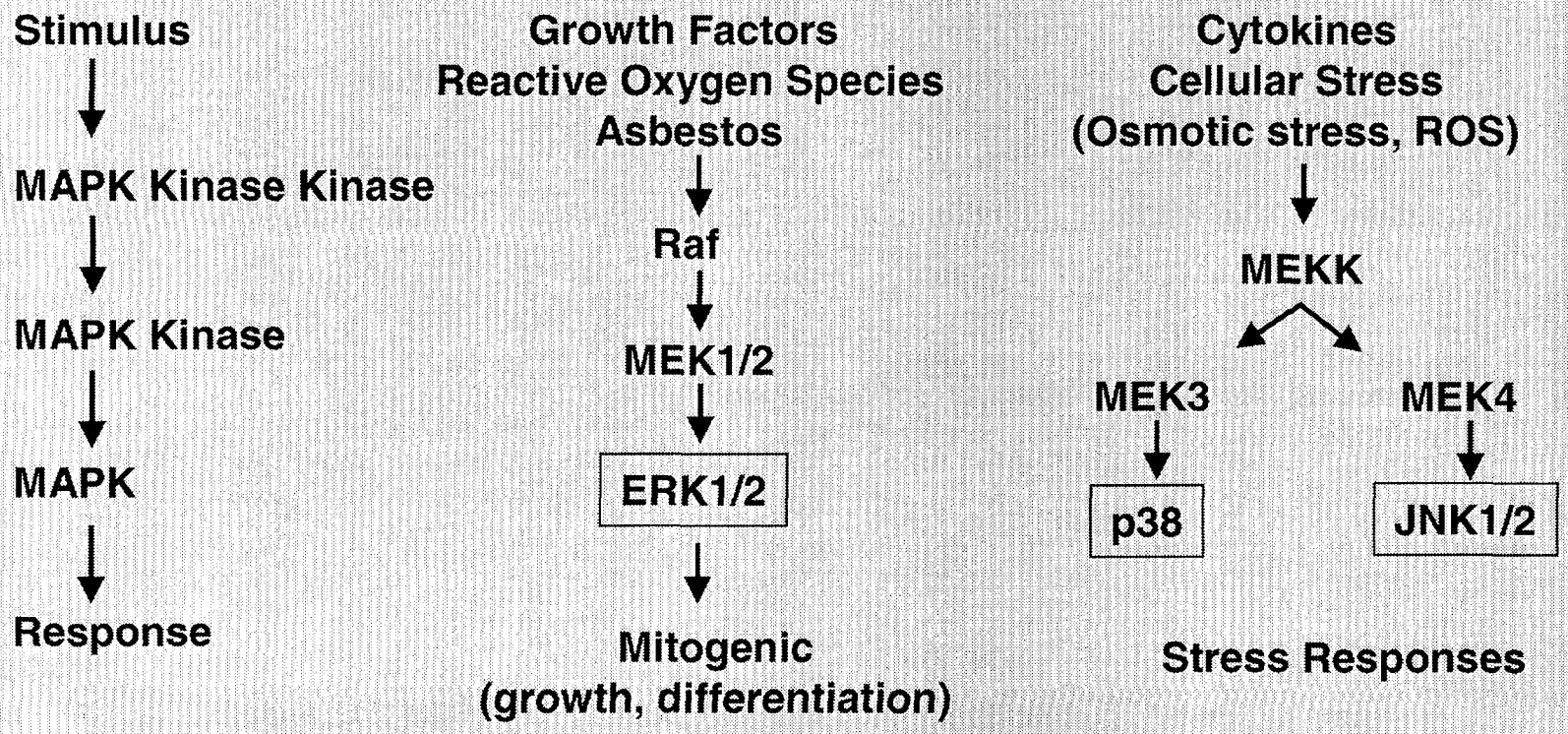
Asbestos-Induced AP-1 Activity in Mesothelial Cells



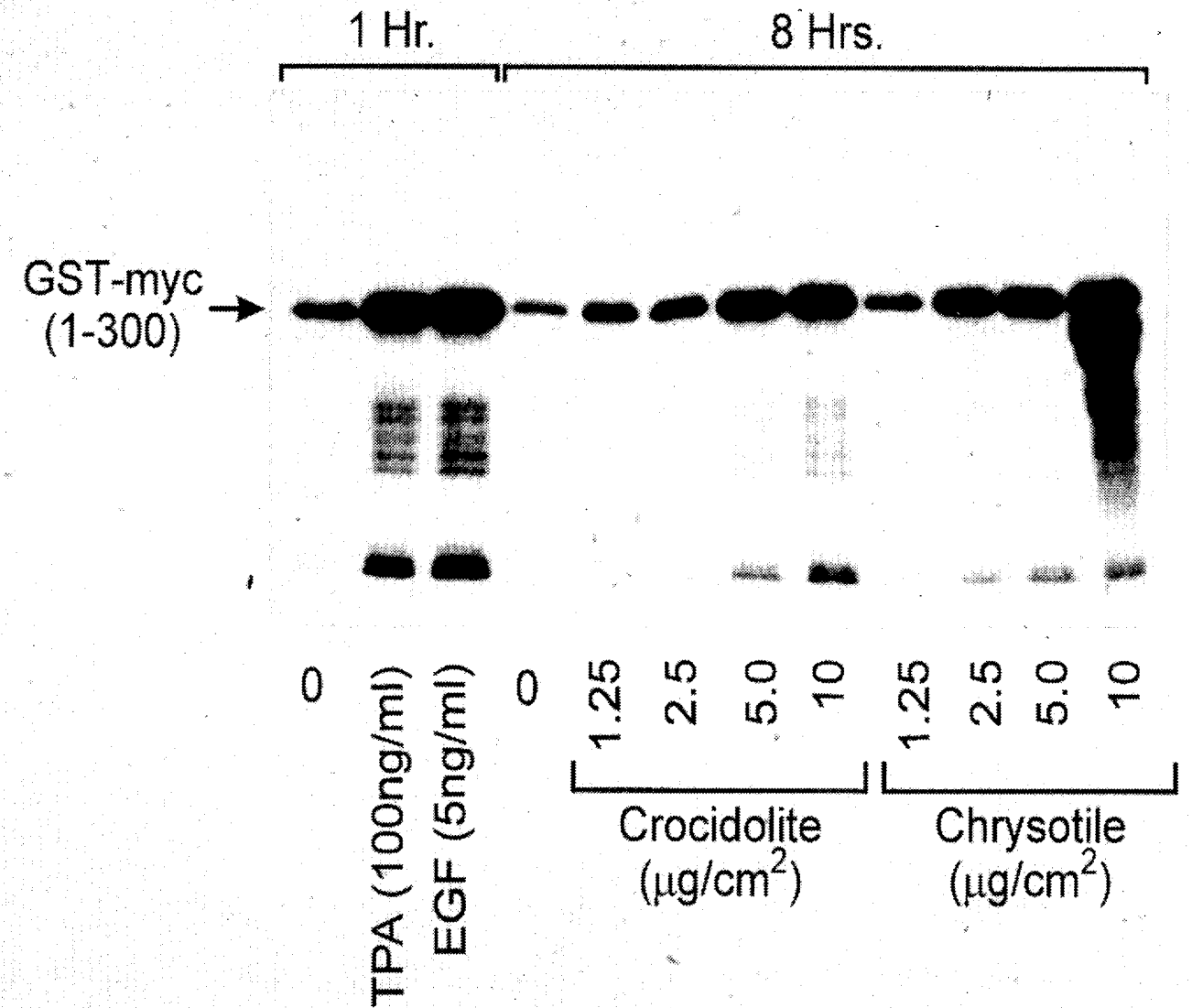

Transition of the G1 phase
DNA replication
Asbestos fibers
MAPK
c-fos
c-jun
Cell proliferation
Signal transduction
Persistent induction of early response genes
Apoptosis
Disease

MITOGEN-ACTIVATED PROTEIN KINASE (MAPK) CASCADE

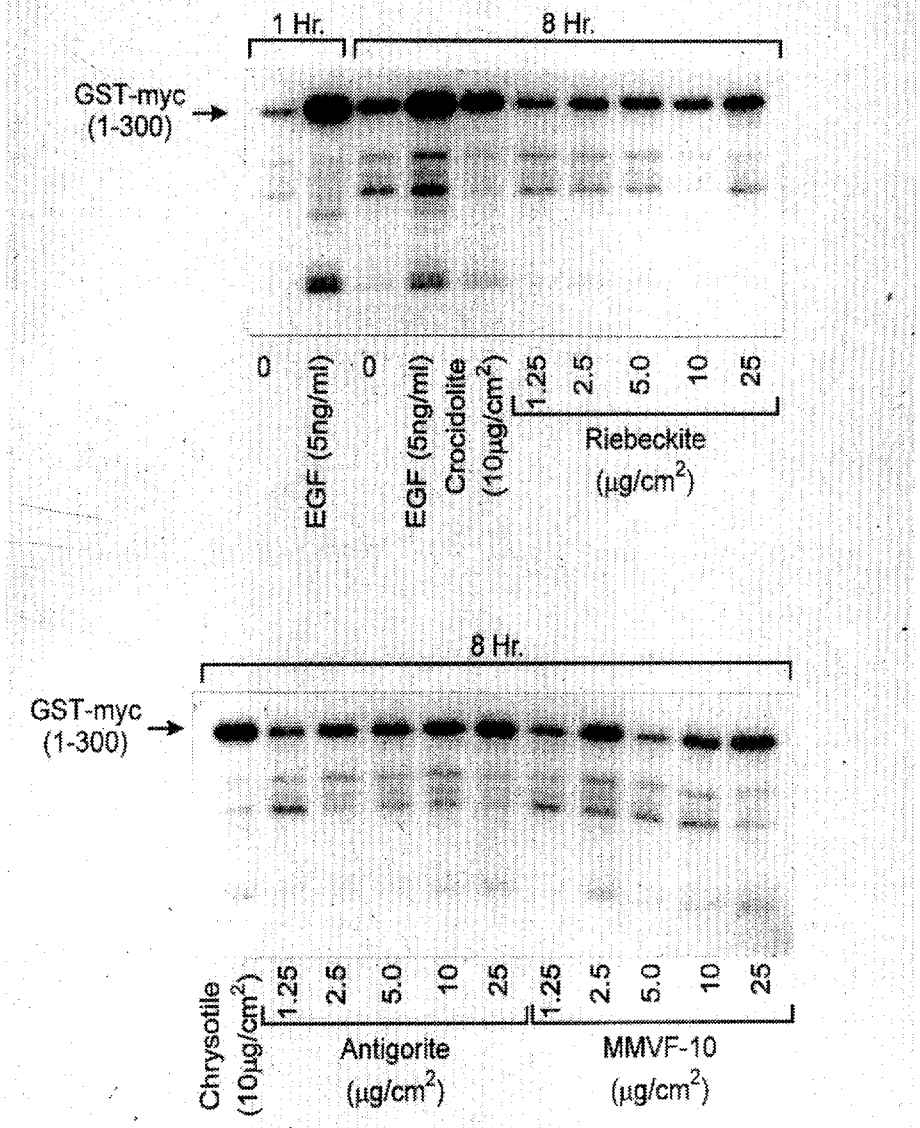
* ERK=Extracellular Signal-Regulated Kinase
* JNK=c-Jun N-terminal Kinase
* p38



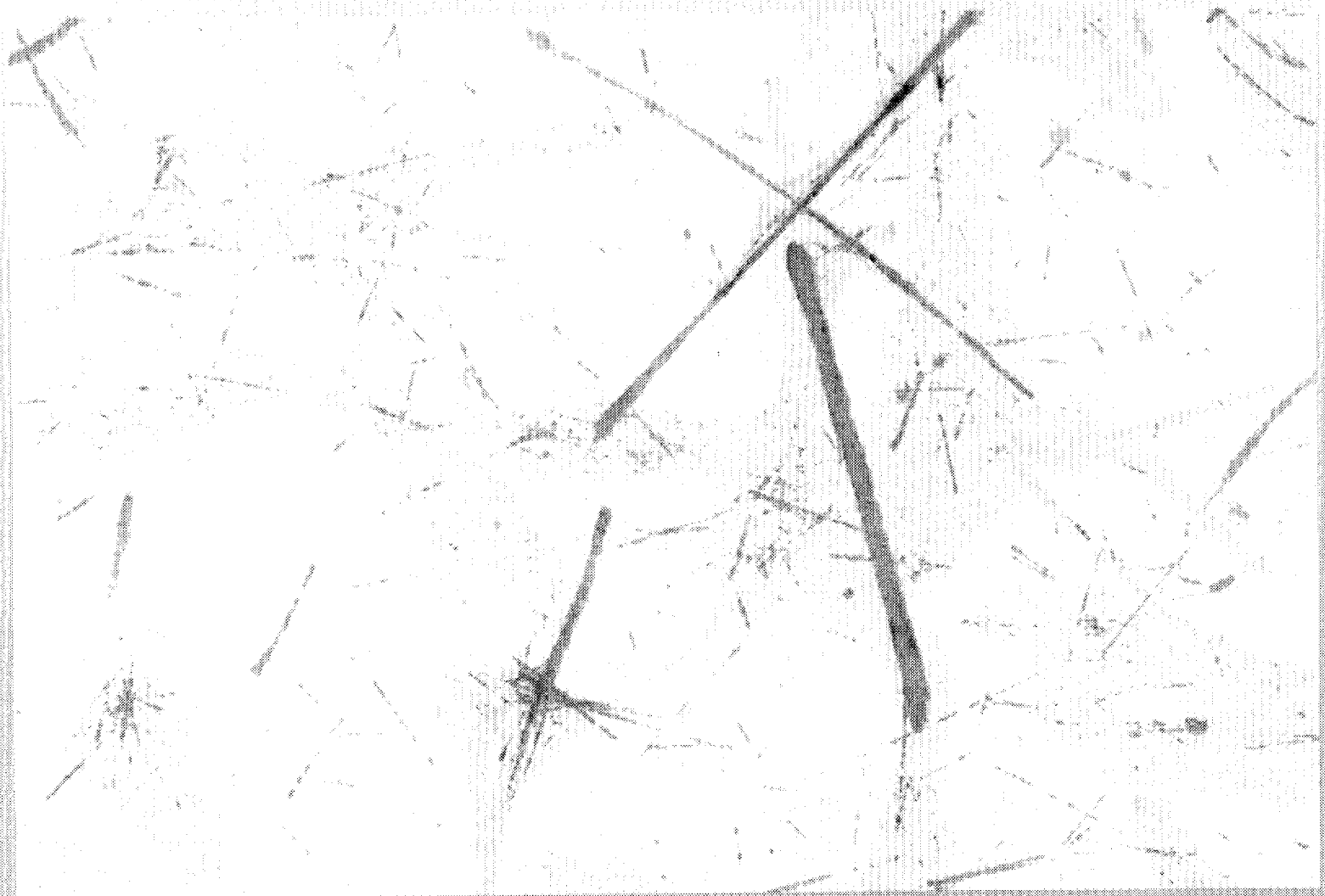
MAP KINASE ACTIVITY IN RAT PLEURAL MESOTHELIAL (RPM) CELLS



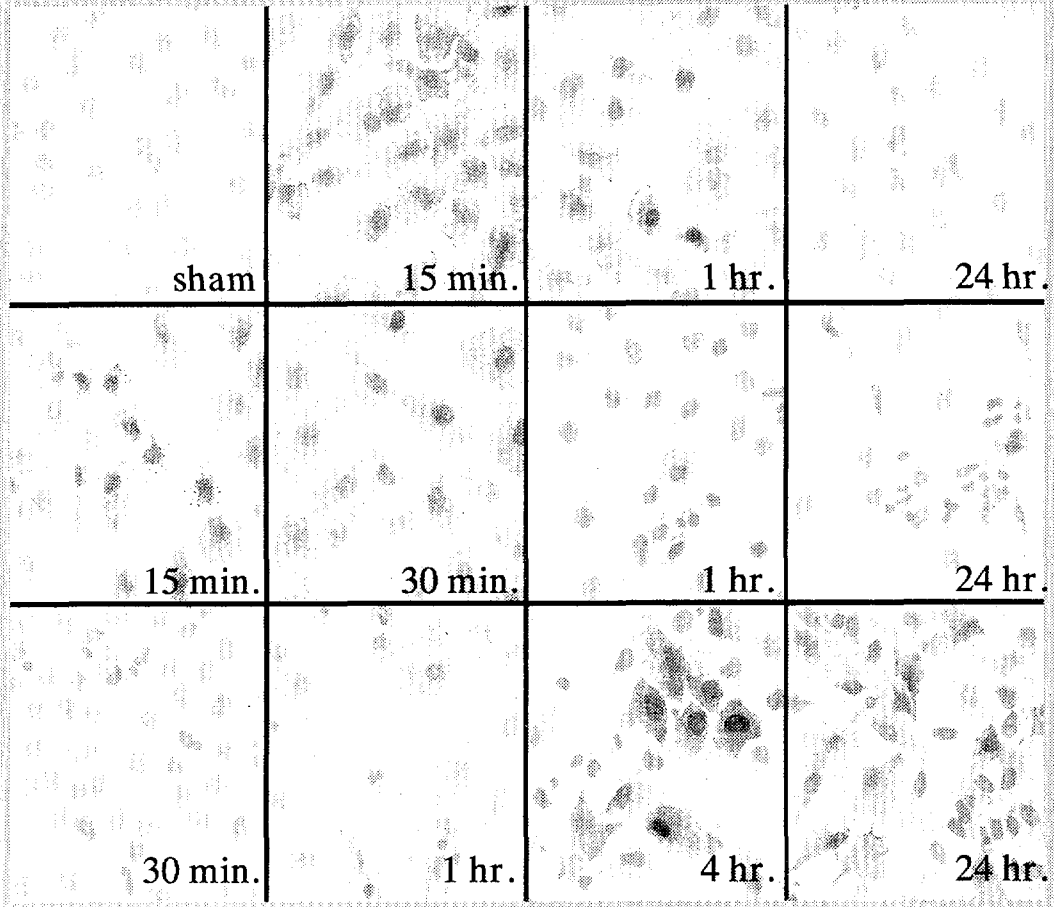
erk2 ACTIVITY IMMUNOPRECIPITATED FROM RAT PLEURAL MESOTHELIAL (RPM) CELLS



Human Met 5A Cells - Merged Confocal Images of EGF-R (Red) and Asbestos Fibers (Green)

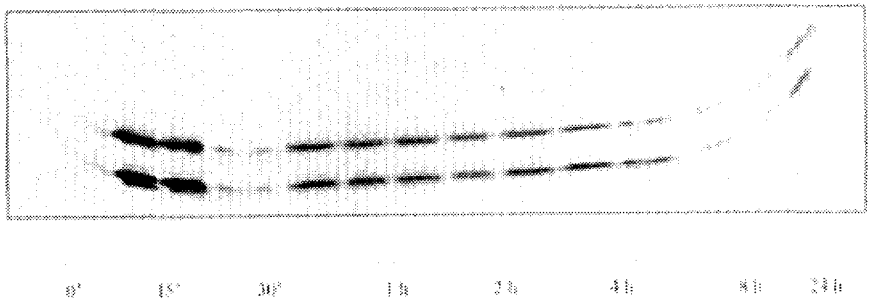


Phospho-ERK in Lung Epithelial Cells

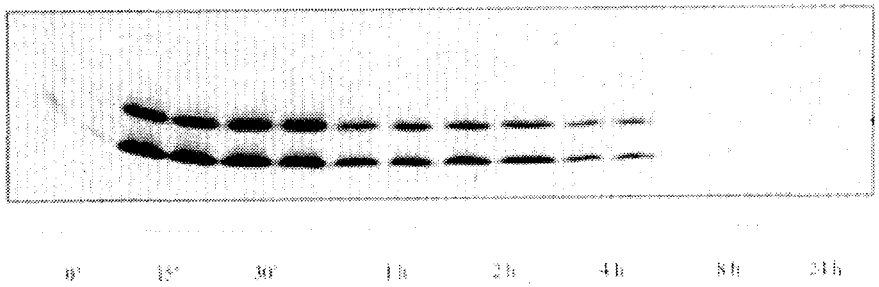


Western Blot for Phospho-ERKs

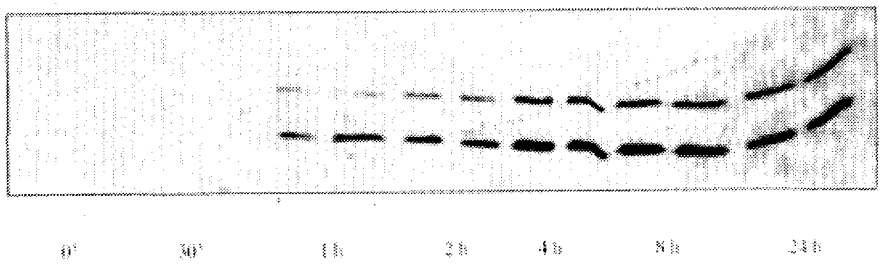
EGF



H_2O_2

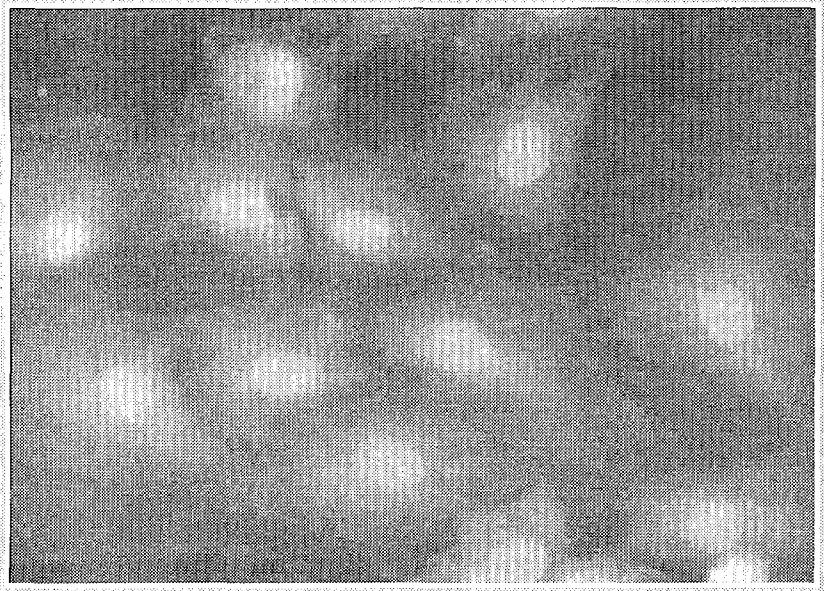


Asbestos

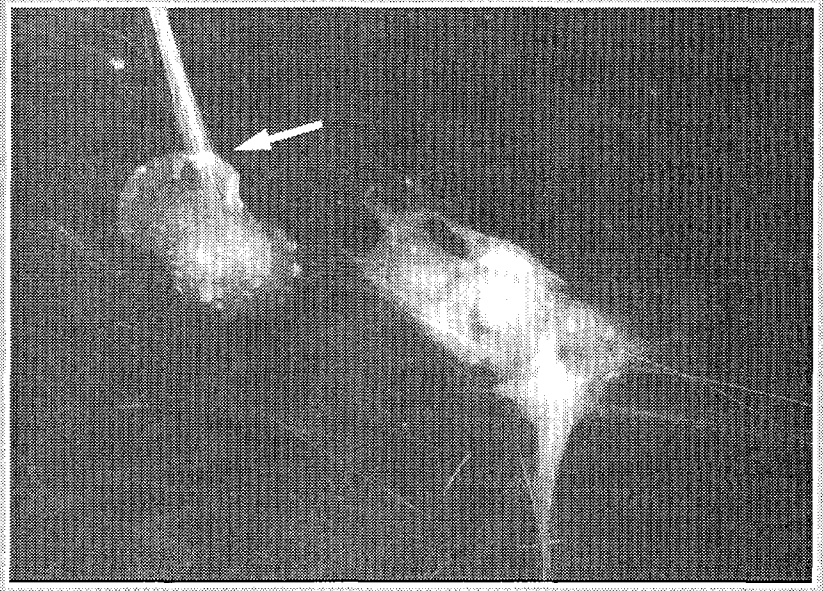


Immunoperoxidase Technique to Determine Changes in Cellular Distributions of Phosphorylated ERKs Following Exposure to Asbestos

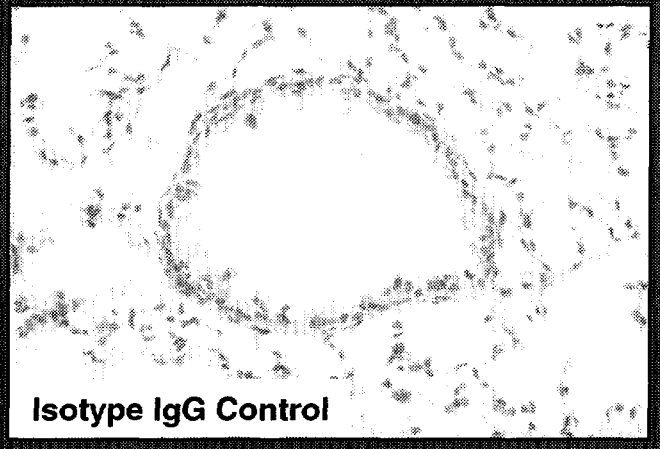
A. Control Cells

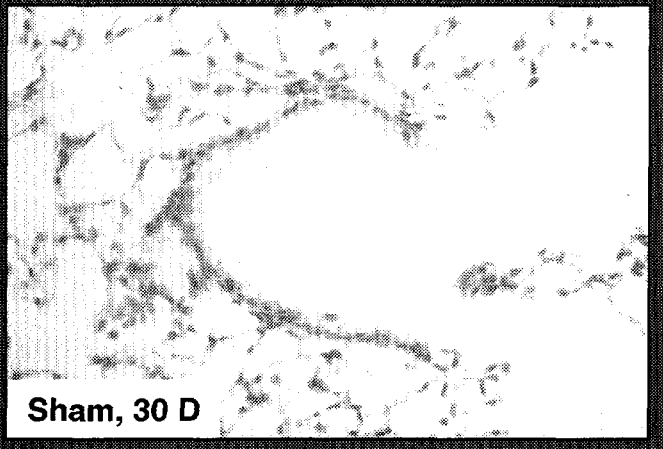


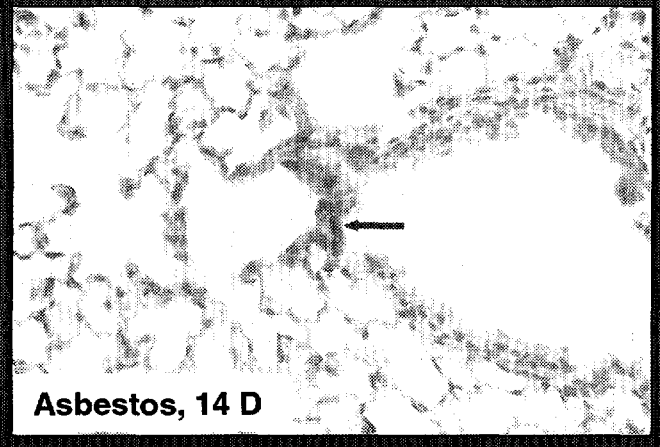
B. Asbestos-exposed Cells

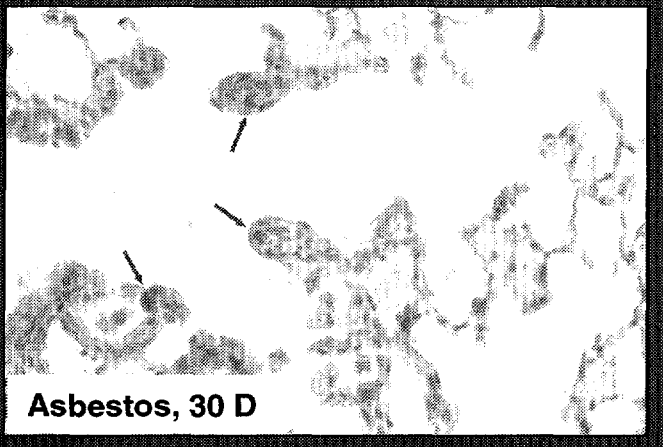


Immunohistochemical Localization of ERK Phosphorylation

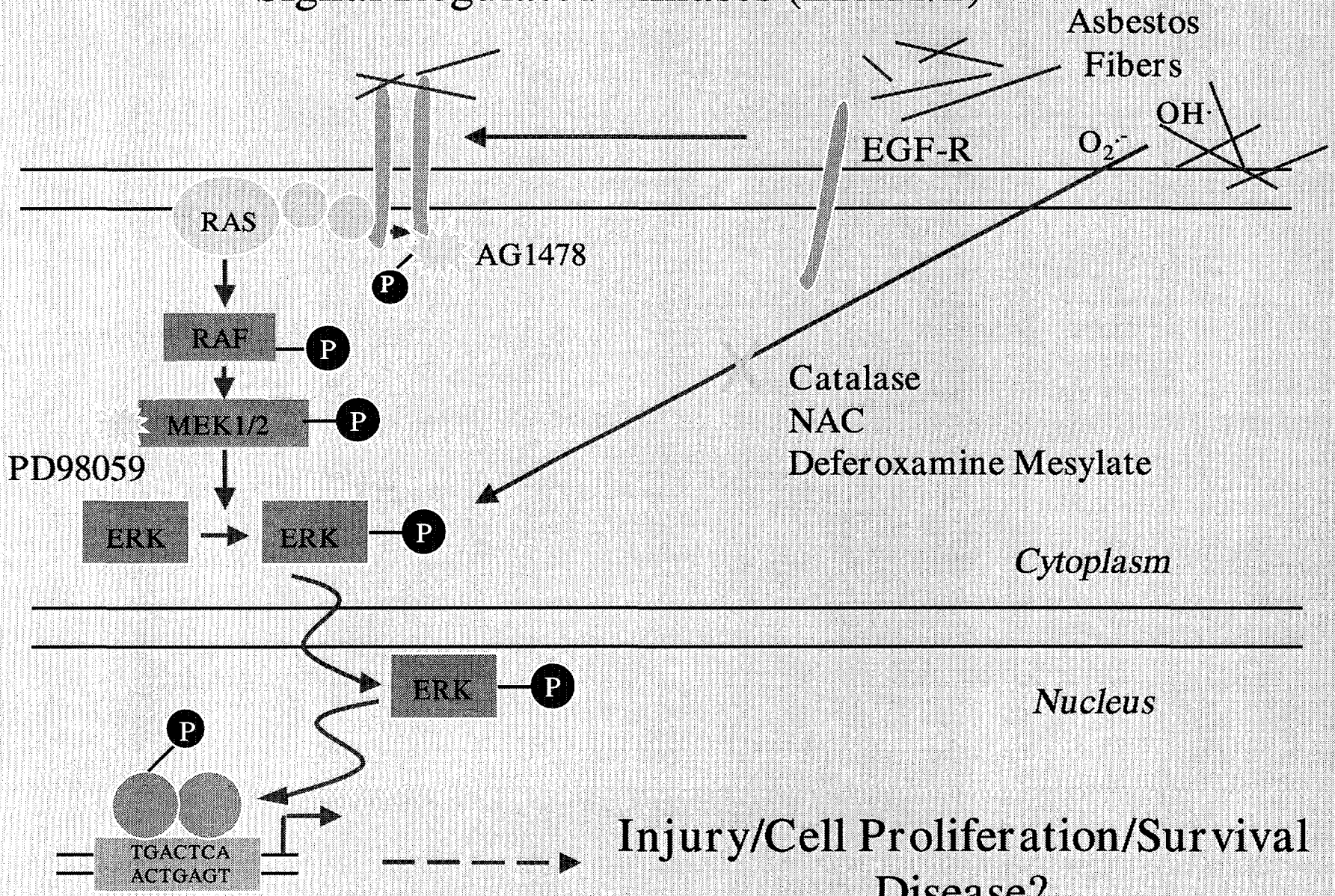








Asbestos-Induced Stimulation of Extracellular Signal Regulated Kinases (ERK1/2)



ASBESTOS HEALTH EFFECT COLLOQUIUM
EPA, Oakland CA, 24-25 May 2001

The physical and chemical properties of asbestos fibers which contribute to biological activity

Bice Fubini, Università di Torino (Italy), Department of Chemistry IFM and Interdepartmental Center "G. Scansetti" for Studies on Asbestos and other Toxic Particulates

In spite of the massive experimental work on asbestos toxicity, performed in the past 15 years, the pathogenic mechanism/s at the molecular level are still partially obscure. As recently reported by Kamp and Weitzmann (1999), who did pioneering experiments on asbestos mechanisms, "*...no single mechanism fully accounts for all the complex biological abnormalities caused by asbestos.*" This is even more so when it comes to the physico-chemical feature/s which impart the carcinogenic potency to asbestos. ***Particulate toxicants***, i.e. toxicant which act as particles and not as a simple molecule (molecular toxicants), such as asbestos fibres, are complex entities. They act through contact between their surface and cells and tissues. The surface is usually different from the bulk, and exhibits reactive sites, whose nature much depends on the history of the sample. Therefore we may have particles with the same nominal composition, but with remarkably different states of the surface, hence toxicity. Moreover the surface may acquire contaminants from the environment and uptake endogenous molecules when within living matter, hence progressively changing its chemical nature. Because of the long biopersistence, several contacts between fibers and cells may take place in different biological compartments, not necessarily involving the same surface chemical functionalities.

On the basis of experimental finding and epidemiological studies, three main factors appear to contribute to asbestos related health effects: i, the ***form*** of the fiber, ii, the ***mineralogical, chemical and surface composition***, iii, the ***biopersistence*** (Fubini and Otero-Aréan, 1999). These features will be examined separately and analyzed on the basis of the five mechanisms of fiber carcinogenesis reported by Kane et al. (IARC1996).

Long thin fibers are more potent than short ones or isometric analogues. Factor accounting for this are: deposition, easier translocation to the pleura, frustrated phagocytosis, inhibition of clearance, and, in some cases, different surface behavior. Few attempts have been made to investigate which, of the biochemical and cellular responses elicited by asbestos fibers, depend upon fibrous habit and size. Mossman and coworkers have compared fibers with non-fibrous analogues and Davis and coworkers short and long fibers from the same batch. Fibres were more effective than non-fibrous materials, in all the cases examined, except in NO induction (Quinlan et al., 1998); long fibres were always more biologically active than short ones. Some chemical properties, however, were different in short and long fibers (Donaldson et al., 1995; Graham et al., 1999). Surface properties of the non–fibrous analogues were not reported in the relevant papers. More data, from several well characterized sources of materials, are required to discriminate which biological response is related to the physical or to the chemical nature of the fibers.

The composition of the mineral comprises fibrous and non fibrous mineral contaminants, chemical composition of the fiber, state of the surface and surface contamination by exogenous and endogenous matter. As numerous *in vitro* and *in vivo* studies indicate a prominent role of iron catalyzed generation of ROS (Reactive Oxygen Species) and, more recently, RNS (Reactive Nitrogen Species) in the mechanisms of asbestos toxicity (reviewed by Hardy and Aust, 1995; Kamp and Weitzman, 1999), attention needs to be focussed on the iron ions at the fiber surface. Iron may be constitutive of the mineral (crocidolite, amosite, actinolte and antofillite), substitute for magnesium ions (chrysotile, tremolite), or be deposited exogenously/endogenously. The effects caused by iron do not relate with the total iron content (Fubini et al. 1995, Fubini 1996). Iron may be mobilized by chelators or cells (Chao et al, 1994; Chao & Aust, 1994) or be deposited (Shen et al., 2000) Only if iron at the surface is poorly coordinated it may be easily mobilized by endogenous chelators or act at the surface, as a persistent center for the catalysis of ROS. Iron cycling at the fiber surface, as well as a catalytic mechanism of ROS generation, provide chemical systems whose action may continue as long as the

fiber is present, thus accounting for the long latency of asbestos related health effects. Two separate surface sites generate the HO° radical from H_2O_2 or cleave hydrogen-carbon bonds (Fenoglio et al., in press). Iron ions at the solid surface fix irreversibly NO molecules (Martra et al., 1999), suggesting possible interference with iNOS activation. All these effects are modified by thermal or chemical modification of the surface (Otero Arèan et al., 2001; Fenoglio et al., in press). Iron deposition to form asbestos bodies was regarded as defense mechanism towards the fibers. It is a process fiber-selective, as it mostly occurs with long amphiboles fibers. Whether deposited iron is still active is under debate, as contrasting results have been reported (Lund et al., 1994; Ghio et al., 1997). Ferritin, however, was found to adsorb strongly on crocidolite and amosite, be modified and cause significant damage to DNA in presence of ascorbic acid (Fubini et al., 1997; Otero Aréan et al., 1999). This result is in agreement with the increased DNA damage found for amosite-core asbestos bodies, when compared to the effect produced by the naked fiber (Lund et al., 1994).

Biopersistence, is not merely linked to solubility in an aqueous medium. It depends upon deposition, clearing efficiency, which is in turn related to surface properties. *In vivo* extensive reaction with endogenous materials may take place. Both glutathion and ascorbic acid (Brown et al., 2000; Fenoglio et al., 2001), the two major antioxidant defenses in the lung lining layer, have been reported to react with fibers, thus depriving the body of the defenses against the toxic products of the material itself.

At the present level of knowledge any association between each of the mentioned physical and chemical characteristics and the single health outcomes, lung cancer, malignant mesothelioma, fibrosis and pleural plaque, is obviously tentative and speculative. We may note however that the empirical relationships from epidemiological studies report a linear correlation between cumulative exposure and lung cancer, with tobacco smoking acting synergistically. The slope appears industry-specific but the type of asbestos does not seem to be correlated to lung cancer risk (Boffetta et al., 1998) At the opposite, mesothelioma induction is described by a model involving a power function of time since first exposure and latencies from 20 to 40 years, with a carcinogenic potency on the pleura specific to both, industry and type of asbestos (Boffetta et al., 1998). The fiber characteristics causing the processes yielding these two diseases not necessarily should thus be the same: mineral fibers (asbestos, erionite, ceramic fibers) are the only known cause of mesothelioma, suggesting fibrous habit as a perquisite for this type of diseases. The long latency periods indicate a prominent role of biopersistence while a vast number of experimental studies evidence oxidative damage, see e. g. the development of mesothelioma in p53 deficient mice (Marsella et al., 1997) as one of the key event in the development of the disease. As tremolite, erionite and ceramic fibers, which are potent carcinogens for the pleura, do not virtually contain any iron, the oxidative damage will be sustained by few iron traces at the fiber surface, acting as catalysts for ROS generation. Amphiboles, because of their mineralogical structure, are more potent carcinogens than chrysotile. Conversely lung cancer, which is usually associated to persistent inflammation, may be related to the continuos activation of macrophages and PMN by the fiber burden, generating growth factors (fibrosis), inflammatory cytokines, and radicals arising form reactions among fiber derived radical species and cell derived ROS and RNS. Beside deposition and frustrated phagocytosis, any additional role of the fibrous habit in lung cancer still needs to be elucidated. As all asbestos appear nearly equally potent, length and form of the fiber appear non-influent on the outcome of the disease.

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Lund L.G., Williams M.G., Dodson R.F., Aust A.E., Iron associated with asbestos bodies is responsible for the formation of single-strand breaks in phi-x174-Rfi DNA *Occup. Environ. Med.,* 1994; 51,:p. 200-204.

Marsella JM; Liu BL; Vaslet CA; Kane AB Susceptibility of p53-deficient mice to induction of mesothelioma by crocidolite asbestos fibers. *Environ Health Perspect* 1997; 105, Suppl 5: p. 1069-1072.

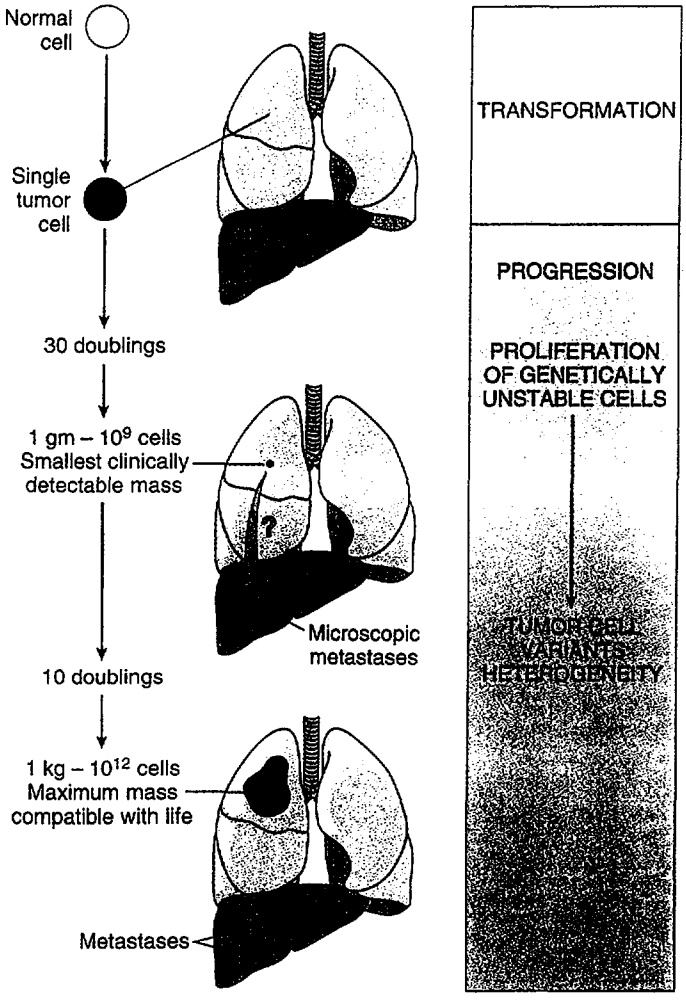
Martra G., Chiardola E., Coluccia S. et al., Reactive sites at the surface of crocidolite asbestos *Langmuir* 1999; 15: p. 5742-5752.

Otero Arèan, C., F. Barcelò, B. Fubiniet al., Free radical activity of natural and heat treated amphibole minerals; *J. In.Biochem.* 2001; 83; p. 211-216.

Quinlan T.R., BeruBe K.A., Hacker M.P., Taatjes D.J., et al., Mechanisms of asbestos-induced nitric oxide production by rat alveolar macrophages in inhalation and in vitro models. *Free Radic. Biol. Med.*, 1998; 24: p.778-788.

Shen Z, Bosbach D, Hochella MF, et al. Using in vitro iron deposition on asbestos to model asbestos bodies formed in human lung. *Chem Res Toxicol,* 2000; 13(9): p. 913-21.

No info. from lumens-
about molecular level
reactions to asbestos.

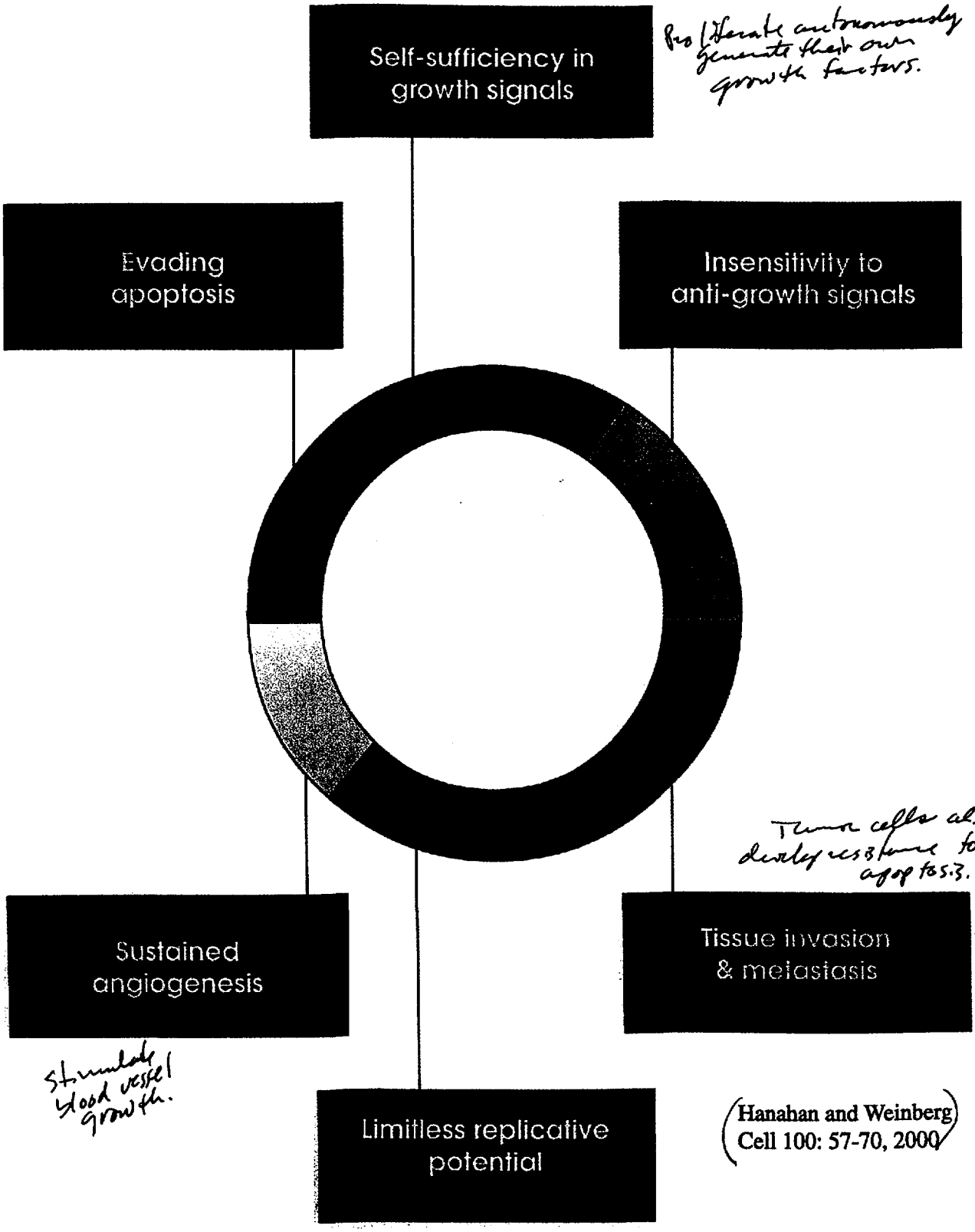


→ ↓ ability to invade and metastasize.

* This question - are we looking for genotoxic.

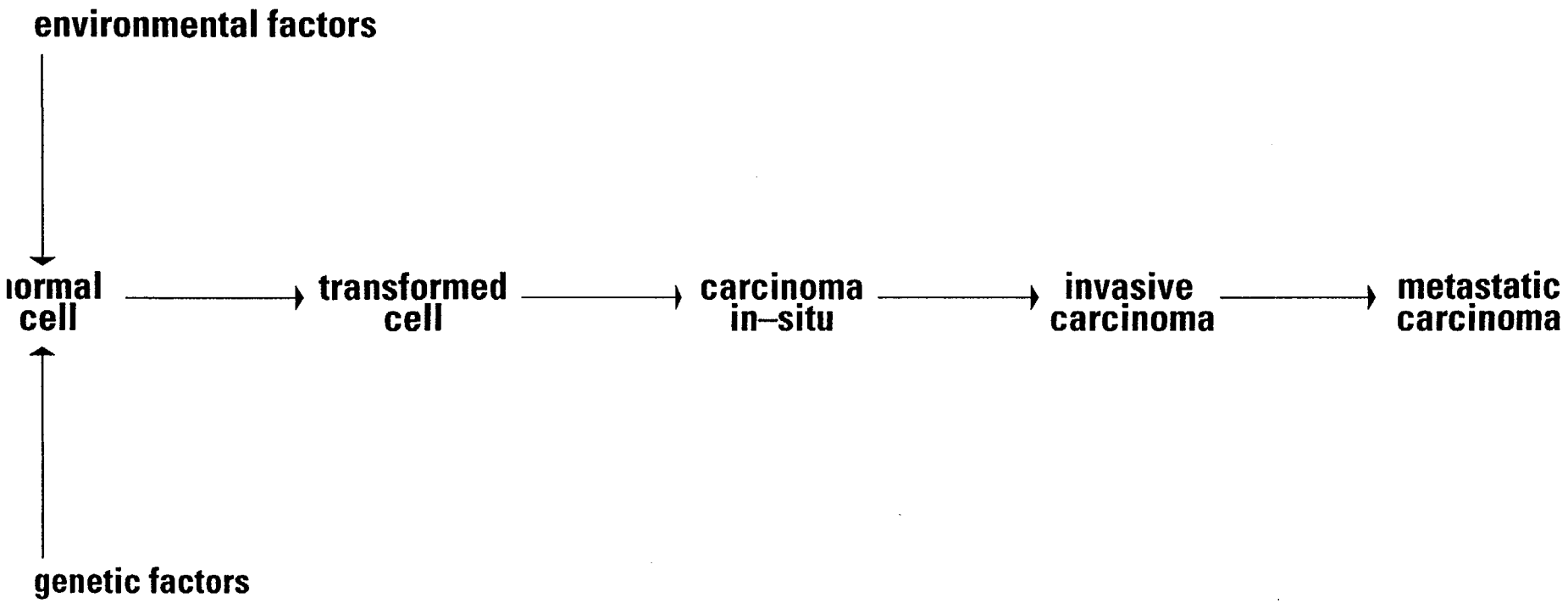
Driving force behind these characters is at a genetic level. *

The Hallmarks of Cancer



Hanahan and Weinberg
Cell 100: 57-70, 2000

Multiple Stages in the Development and Progression of Cancer



Direct Mechanisms of Asbestos Carcinogenesis

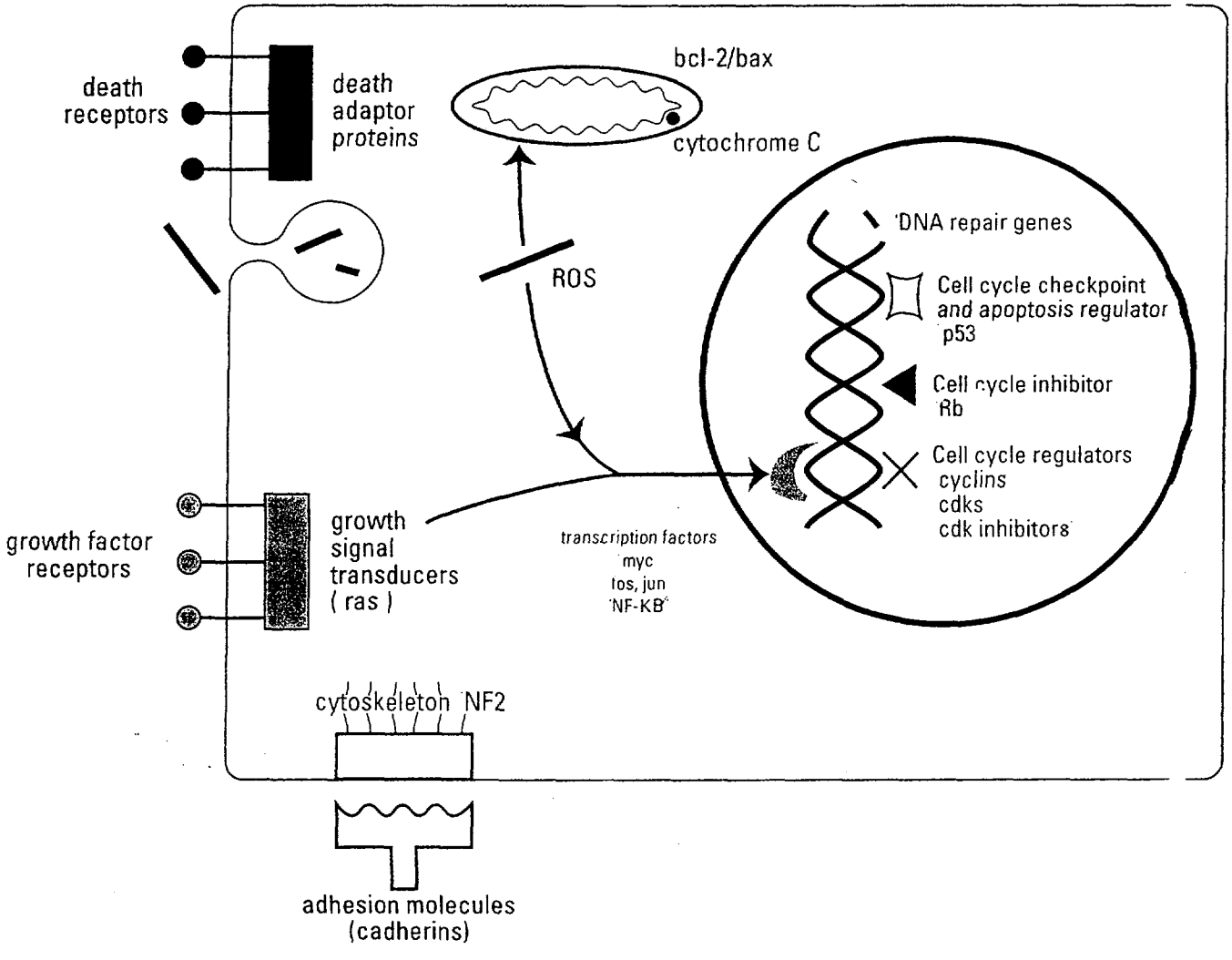
Mechanism	Experimental End-points
Genotoxic	Oxidized bases DNA breaks Mutations – in certain marker genes. Aneuploidy
Non-genotoxic	
Cytotoxic	Induction of apoptosis Induction of necrosis
Mitogenic	Target cell proliferation Activation of surface receptors Induction of growth factor expression Activation of signal transduction pathways

BRONCHOGENIC CARCINOMA

- responsible for majority of asbestos - related deaths
- cigarette smoking and asbestos exposure greatly increase the risk of bronchogenic carcinoma
- latency of 10-30 years
- possible increased risk with asbestosis

Histologic Subtypes of Human Lung Cancer

Subtype	% of Histologic Subtype	
	Smokers (n=2708)	Non-smokers (n=218)
Bronchioloalveolar carcinona	71	29
Adenocarcinoma	82	18
Small cell carcinoma	99	1
Large cell carcinoma	93	7
Squamous cell carcinoma	98	2


death
receptors
death
adaptor
proteins
bcl-2/bax
cytochrome C
ROS
DNA repair genes
Cell cycle checkpoint
and apoptosis regulator
p53
Cell cycle inhibitor
Rb
Cell cycle regulators
cyclins
cdks
cdk inhibitors
growth factor
receptors
growth
signal
transducers
(ras)
transcription factors
myc
fos, jun
NF-KB
cytoskeleton
NF2
adhesion molecules
(cadherins)

Frequent Alterations in Oncogenes in Human Lung Cancer

Oncogene	% of Tumors with Histologic Subtype	
	Small Cell Carcinoma	Non-Small Cell Carcinoma
K-*ras*	rare	20-50
myc	11-50	11
C-*erb* B-2 (Her-2/*neu*)	rare	30
mdm 2	rare	rare

Frequent Alterations in Tumor Suppressor Genes in Human Lung Cancer

Tumor Suppressor Gene	% of Tumors with Histologic Subtype	
	Small Cell Carcinoma	Non-Small Cell Carcinoma
RB	80	20
p53	80	60
NF2	none	none
p16	20	70
FHIT	10	50

Indirect Mechanisms of Asbestos Carcinogenesis

Co-factor with cigarette smoke or viruses

Chronic or persistent inflammation with release of cytokines and growth factors

Secondary genotoxicity (oxidant stress)

Altered gene methylation

Gene Silencing by Promoter Methylation

death-associated protein kinase (DAP-kinase)

p15 and *p16* tumor suppressor genes

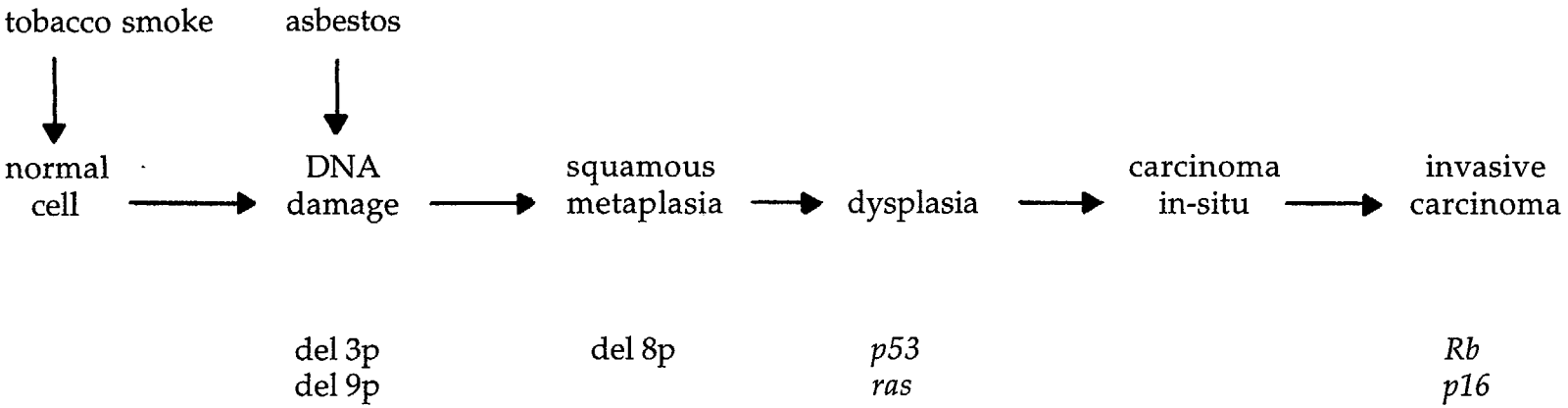
TIMP3

fragile histidine triad (FHIT)

retinoic acid receptor-β

H-cadherin (CDH 13)

PATHOGENESIS OF LUNG CANCER



Ref. Wistuba et al., Cancer Res. 59: 1973-1979, 1999

MALIGNANT MESOTHELIOMA

- rare : 2-20 cases / 10^6 / year

- more common with exposure to amphiboles
  chrysotile factories and mines may be
  contaminated with amphiboles

- latency of 15-60 years

- no association with cigarette smoking or asbestosis

- high incidence in shipbuilding and insulation industries

- difficult pathologic diagnosis

- poor response to therapy

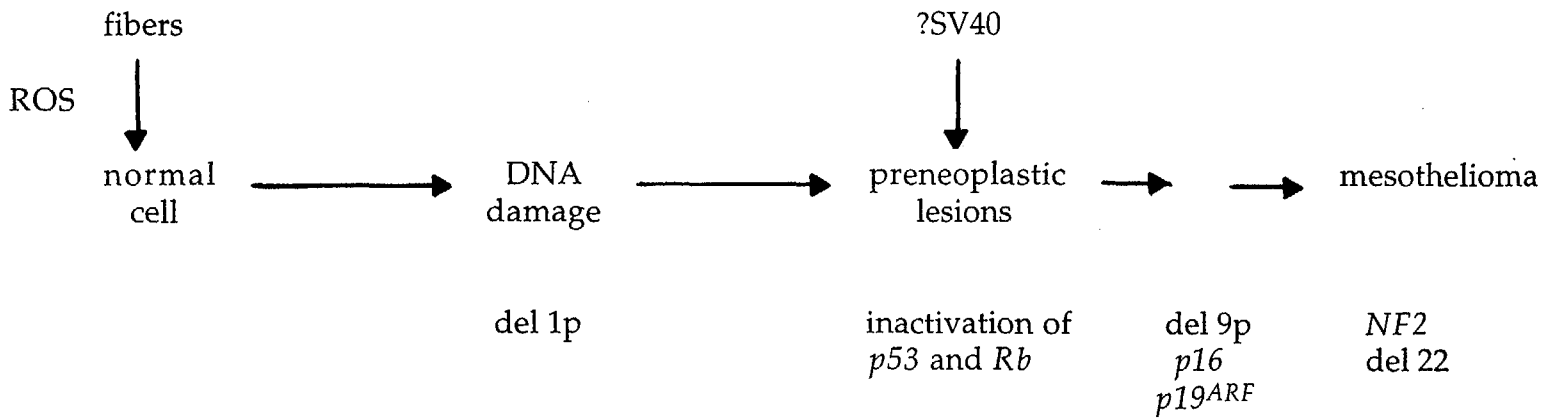
Alterations in Oncogenes in Malignant Mesothelioma

Oncogene	Human	Rat	Mouse
K-*ras*	none	none	?
c-*fos*, c-*jun*	?	?	overexpressed
mdm 2	not amplified	?	?
c-*myc*	overexpressed	?	?

Alterations in Tumor Suppressor Genes in Malignant Mesothelioma

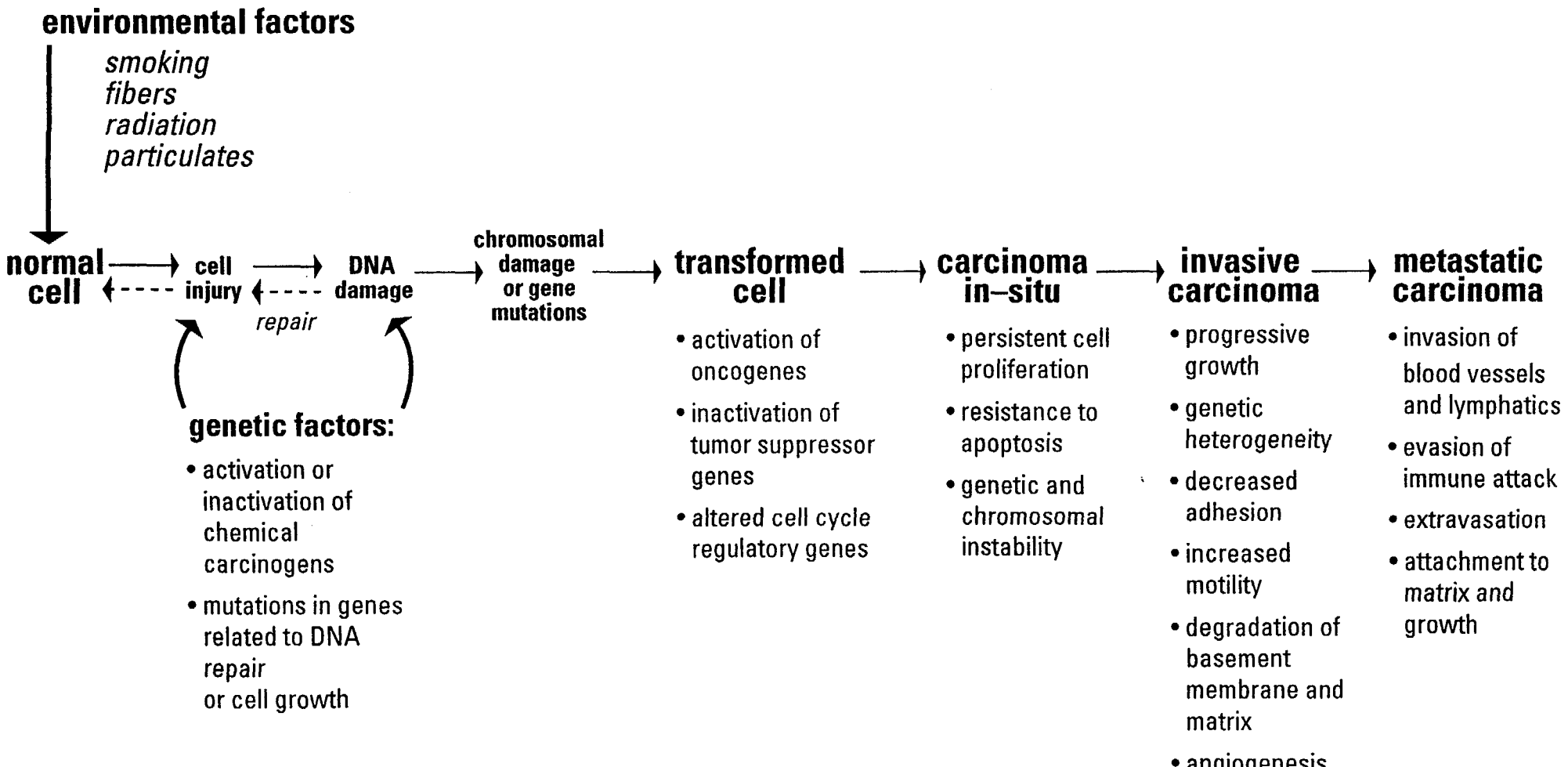
Tumor Suppressor Gene	Human	Rat	Mouse
Rb	none	?	?
p53	overexpressed; rare mutations or deletions	no mutations or deletions	loss of expression; no mutations
NF2	multiple mutations; allelic loss	none	?
$p15^{INK4b}$	deleted (70-100%)	?	deleted (80%)
$p16^{INK4a}$	deleted (70-100%)	?	deleted (80%)

PATHOGENESIS OF MALIGNANT MESOTHELIOMA



Ref. Murthy and Testa, J. Cell. Physiol. 180: 150-157, 1999

Molecular Steps in the Development and Progression of Cancer



Genetic Susceptibility to Lung Cancer

1. Gene polymorphisms involving metabolic activation of carcinogens

   CYP1A1 and squamous cell carcinoma
   CYP2E1 and adenocarcinoma
   (Marchand et al. Cancer Res. 58:4858-4863, 1998)

2. Gene polymorphisms involving detoxification of carcinogens

   GSTM1 null allele and ETS
   (Bennett et al. JNCI 91:2009-2014, 1999)

3. Polymorphisms in tumor suppressor genes

   - *p53* codon 72 (*Arg/Pro*) and adenocarcinoma
     (Fan et al. Cancer Epid. Biomarkers Prev. 9:1037-1042,2000)
   - germ-line *p53* mutations
     (Nichols et al. Cancer Epid. Biomarkers Prev. 10:83-87,2001)

4. Polymorphisms in DNA repair genes

   XRCC1
   XRCC3
   XPD
   (Butkiewicz et al. Carcinogenesis 22:593-597, 2001)

Genetic Susceptibility to Malignant Mesothelioma

1. Li-Fraumeni syndrome—germ-line *p53* mutations
   increased incidence of mesothelioma after radiotherapy for breast cancer
   (Hisada et al. JNCI 90:606-611, 1998)

2. Genetic susceptibility in Cappadocian region of Turkey
   six generation extended pedigree (n = 526)
   22 affected families—41 cases
   autosomal dominant inheritance
   erionite is a potential cofactor
   (Roushdy-Hammady et al. The Lancet 357:444-445, 2001)

Mechanisms of Fiber Carcinogenesis

Co-factor with cigarette smoke

Co-factor with viruses (?SV40)

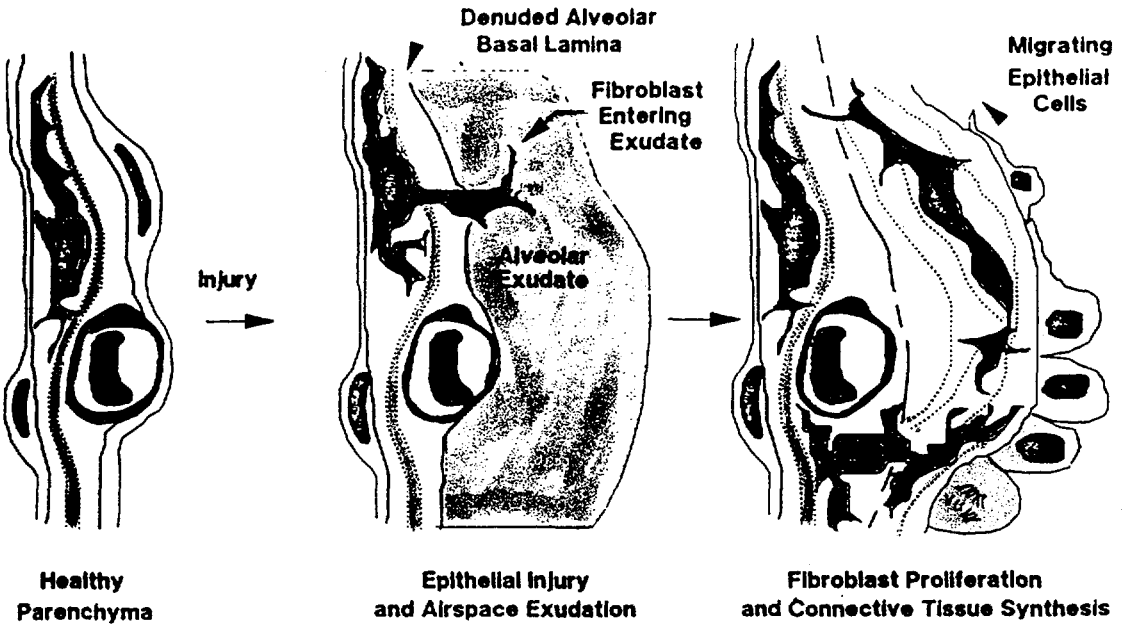
Clastogenic and/or aneuploidogenic

Persistent inflammation: cytokines
growth factors
free radicals from macrophages

Oxidant stress and altered gene expression

Cell proliferation and/or apoptosis

Connective Tissue Remodeling in Pulmonary Fibrosis



Kuhn et al. Am. Rev. Resp. Dis. 140:1693-1703, 1989

MACROPHAGES ARE THE INITIAL TARGET CELLS OF INHALED PARTICLES

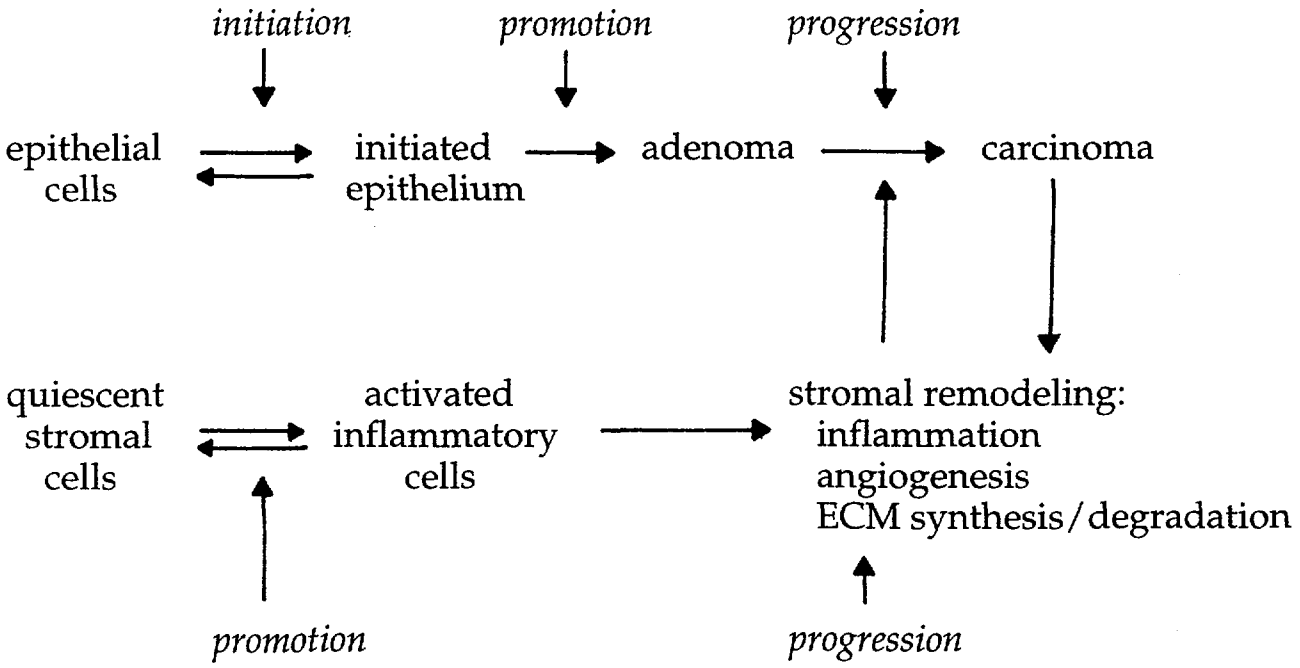
phagocytosis

generation of reactive oxygen metabolites

release of lysosomal enzymes and neutral proteases

release of growth factors for mesenchymal cells

Epithelial—Stromal Interactions in Tumor Progression



(Coussens and Werb, J. Exp. Med. 193:F23-F24, 2001)

Inflammation and Fibrosis in Tumor Progression

- increased expression of CSF-1
- chronic inflammation predisposes to cancer—liver, stomach, urinary bladder, skin
- NSAIDs decrease risk of colon cancer—inhibition of COX-2 and prostaglandin synthesis
- fibrosis predisposes to lung cancer
- upregulated leukocyte adhesion molecules promote metastasis
- MMP-9-deficient mice show decreased angiogenesis and slower tumor progression

Determinants of Asbestos Toxicity

Gene McConnell 5/25/01

— *Same toxicity for all asbestos types?* —

Fiber Characteristics

— 3 "D's"

- *dosimetry; which dosemetric?*
- *short vs. long fibers*
- *biopersistence; chrysotile vs. amphiboles*

Environmental Factors

— mixed exposures

- *fibers and non-fibers*
- *different fiber types*

— occupational *vs.* environmental exposures

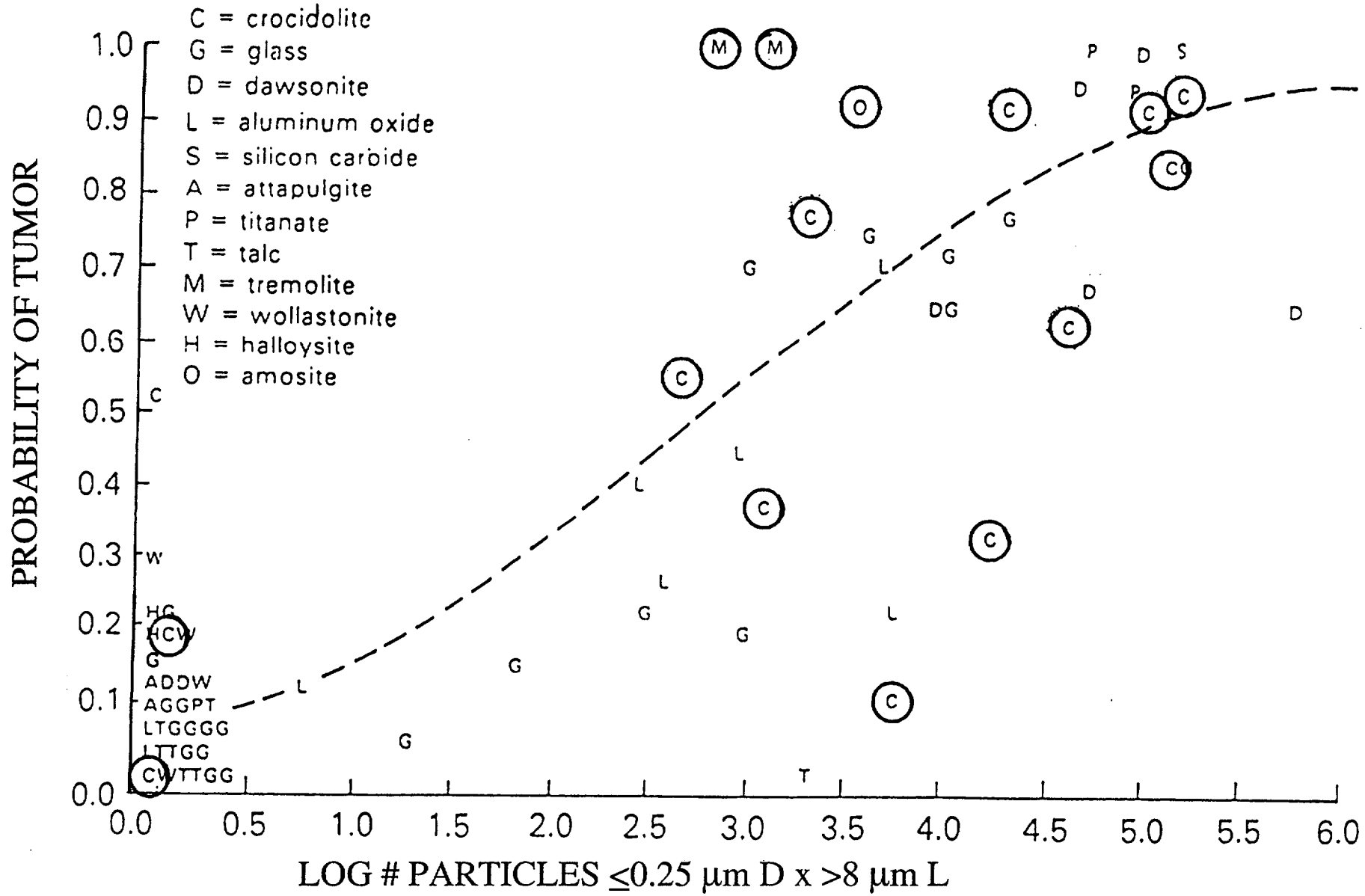
- *cancer, non-cancer effects*

Host Factors

— susceptible populations

- *age*
- *pre-existing conditions*

Stanton *et al.*, 1981: Pleural tumors after 40 mg i.pl. implantation
Carcinogenicity depends on dimension and durability of fibers:
durable, long and thin fibers



Intracavitary Injection Studies

Useful for Risk Assessment?

Caveats: **High dose per surface area** *(inflammation)*

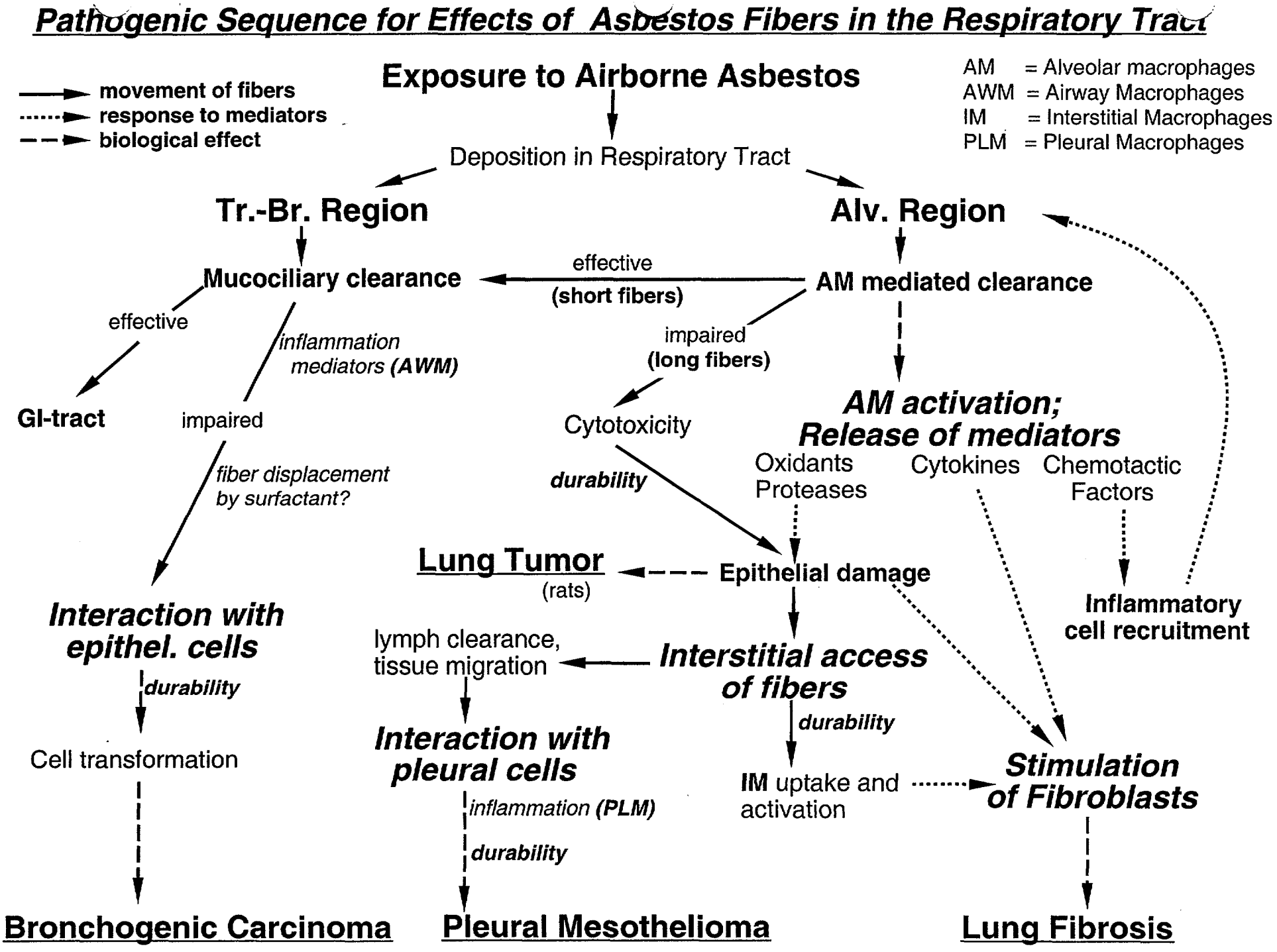
Relevancy for lung tumors? *(diff. cell types; mechanisms)*

Relevancy for mesothelioma? *(fibers have to migrate from alveoli to pleura)*

Intracavitary test will identify:

Potential to induce mesothelioma

Concepts of fiber toxicology


Pathogenic Sequence for Effects of Asbestos Fibers in the Respiratory Tract
movement of fibers
response to mediators
biological effect
Exposure to Airborne Asbestos
AM = Alveolar macrophages
AWM = Airway Macrophages
IM = Interstitial Macrophages
PLM = Pleural Macrophages
Deposition in Respiratory Tract
Tr.-Br. Region
Alv. Region
Mucociliary clearance
effective
(short fibers)
AM mediated clearance
effective
inflammation mediators (AWM)
impaired
(long fibers)
GI-tract
impaired
Cytotoxicity
AM activation; Release of mediators
fiber displacement by surfactant?
durability
Oxidants Proteases
Cytokines
Chemotactic Factors
Lung Tumor
(rats)
Epithelial damage
Interaction with epithel. cells
Inflammatory cell recruitment
lymph clearance, tissue migration
Interstitial access of fibers
durability
Interaction with pleural cells
IM uptake and activation
Stimulation of Fibroblasts
inflammation (PLM)
durability
Cell transformation
Bronchogenic Carcinoma
Pleural Mesothelioma
Lung Fibrosis

Pathogenicity and Fiber Length: The Role of AM Size

Hypothesis: **Phagocytizable fibers ⟶ clearance**
prevention of target cell interaction

Average AM Diameters:

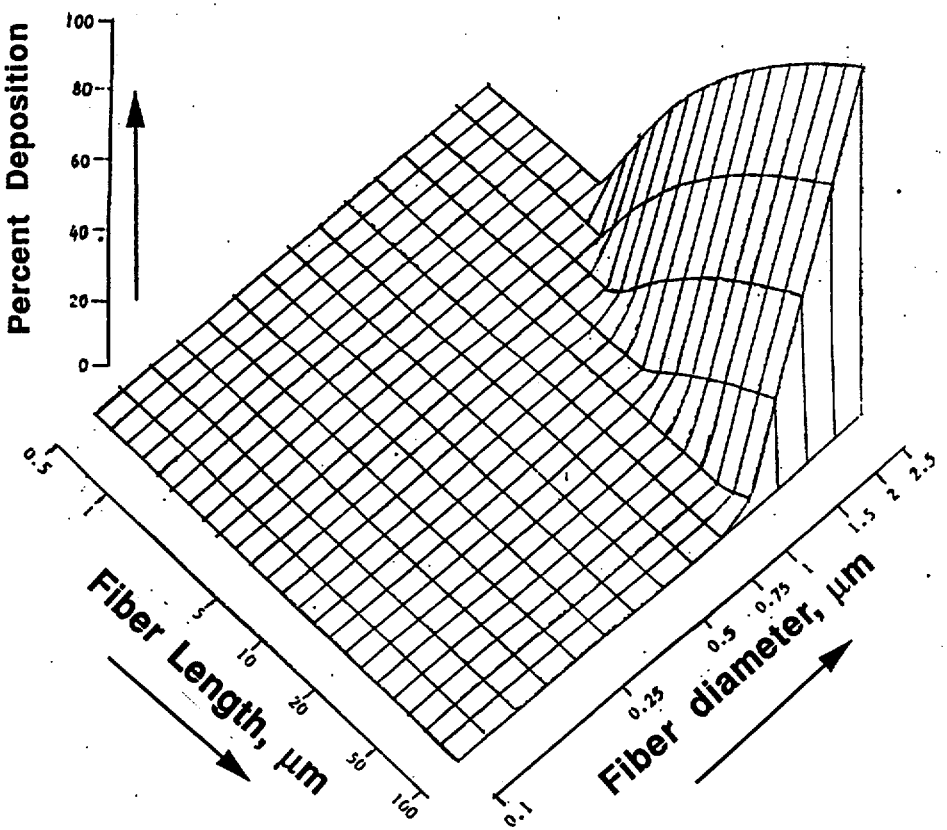
Rat:	**10.5 – 13 μm**	*Crapo et al., 1983; Lum et al., 1983; Stone et al., 1992;*
Human:	**14 – 21 μm**	*Sebring and Lehnert, 1992; Krombach et al., 1997*

For cancer ⟶ number of fibers longer 20 μm

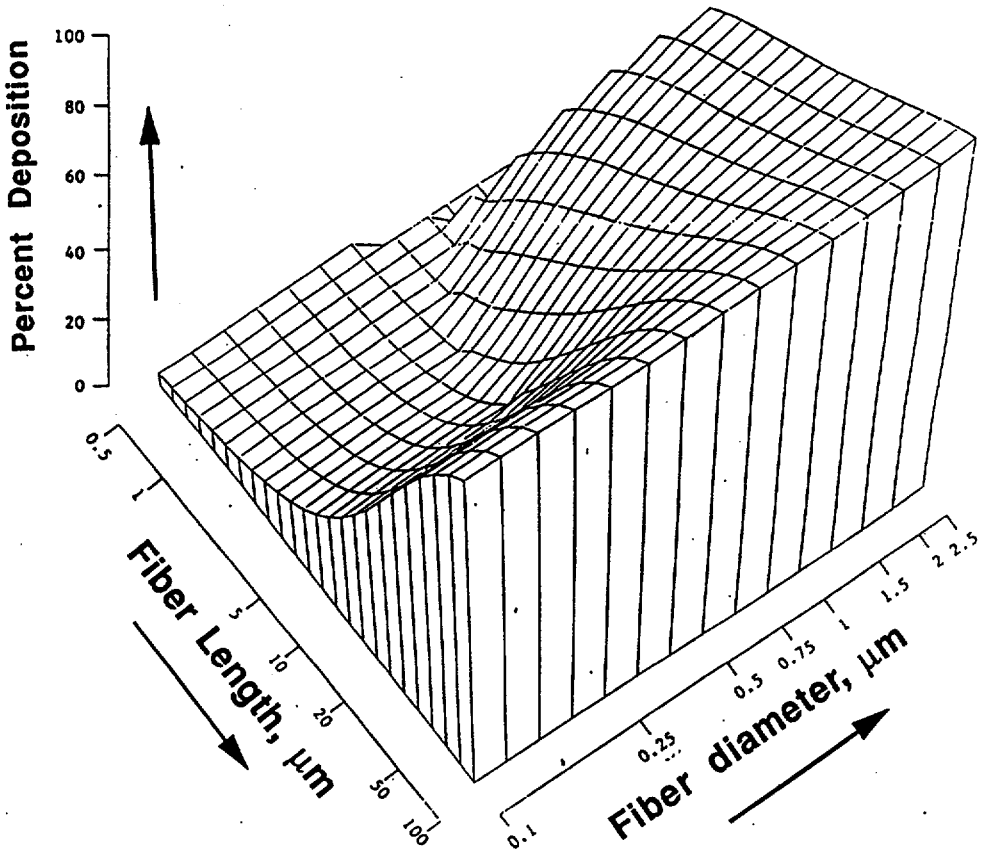
For non-cancer ⟶ all fibers *(but: also impact for tumors!)*

Predicted deposition of fibers in human extrathoracic airways

(after Yu, 1990)



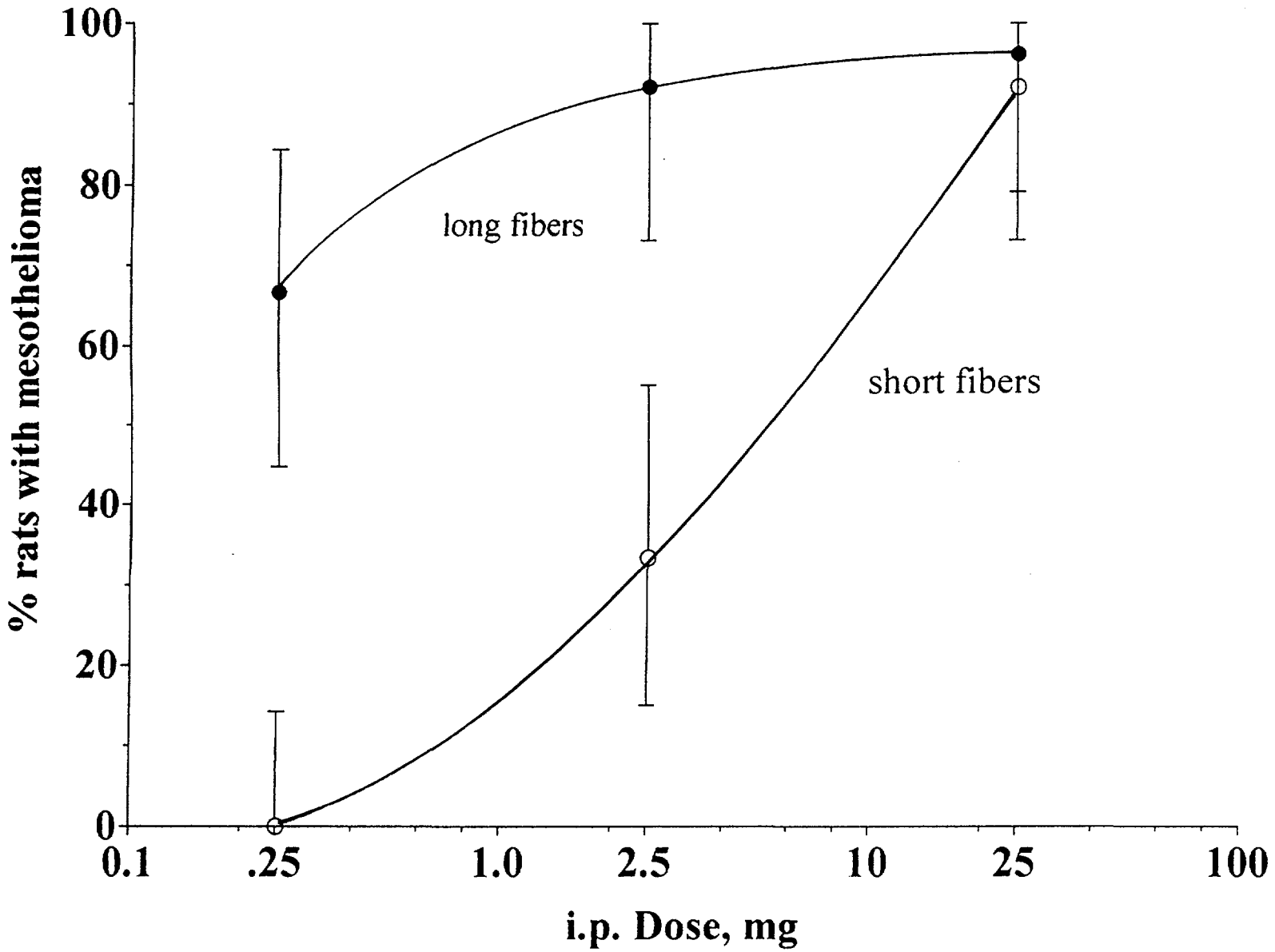
Mouth-breathing

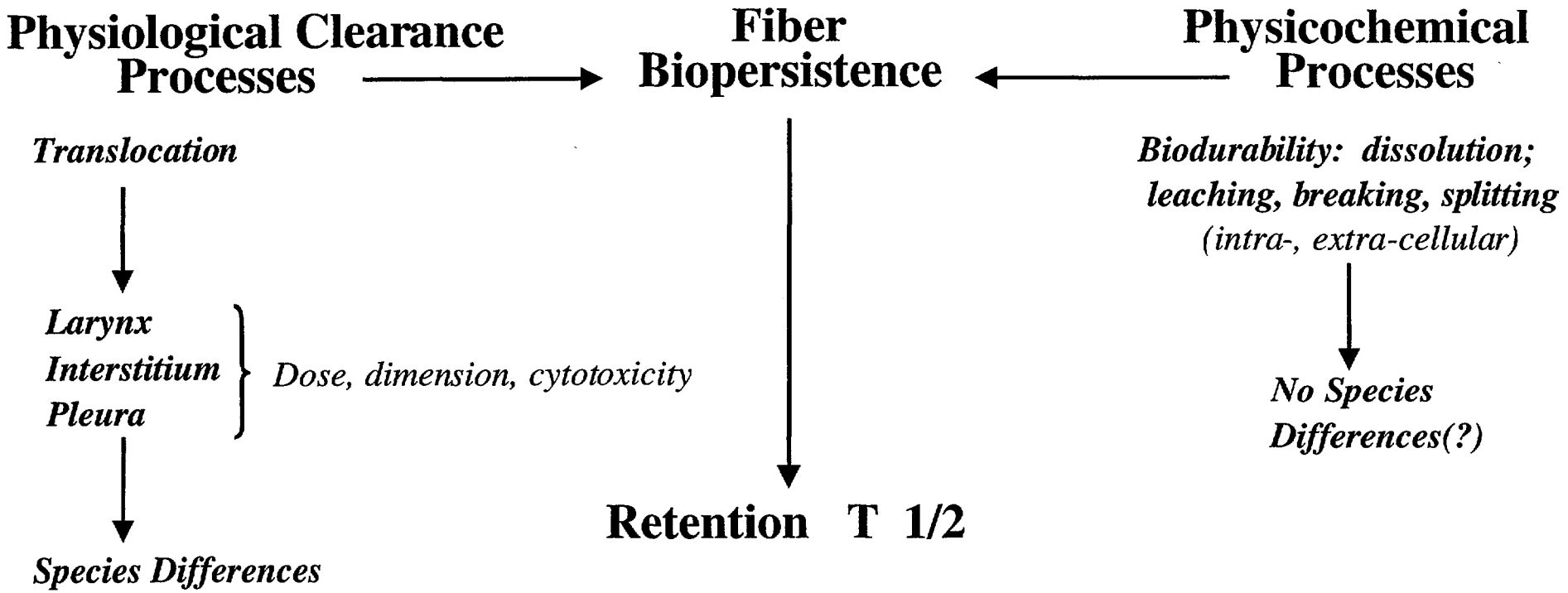


Nose-breathing

Peritoneal mesothelioma After I.P. Injection of Long and Short Chrysotile

(mean and 95% CI) (Davis and Jones, 1988)

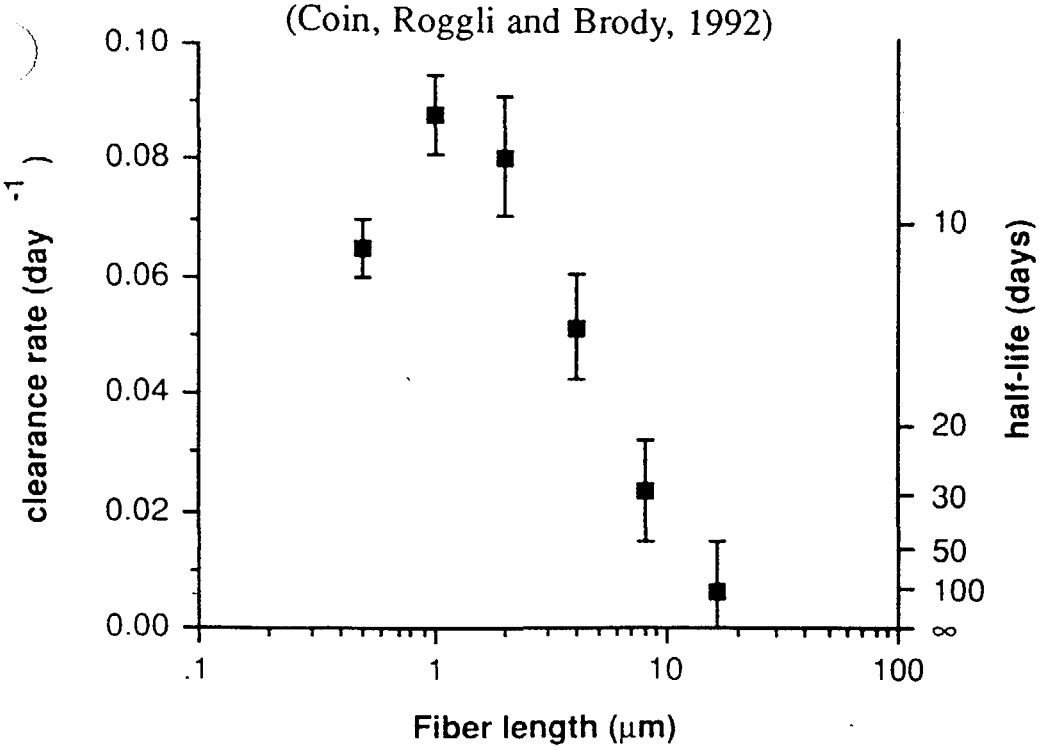




Biopersistence = Biodurability + Physiological Clearance

Clearance of Chrysotile from Rat Lung

(Coin, Roggli and Brody, 1992)



Chronic Inhalation of Asbestos (long fiber studies) in Rats; Effects and Biopersistence

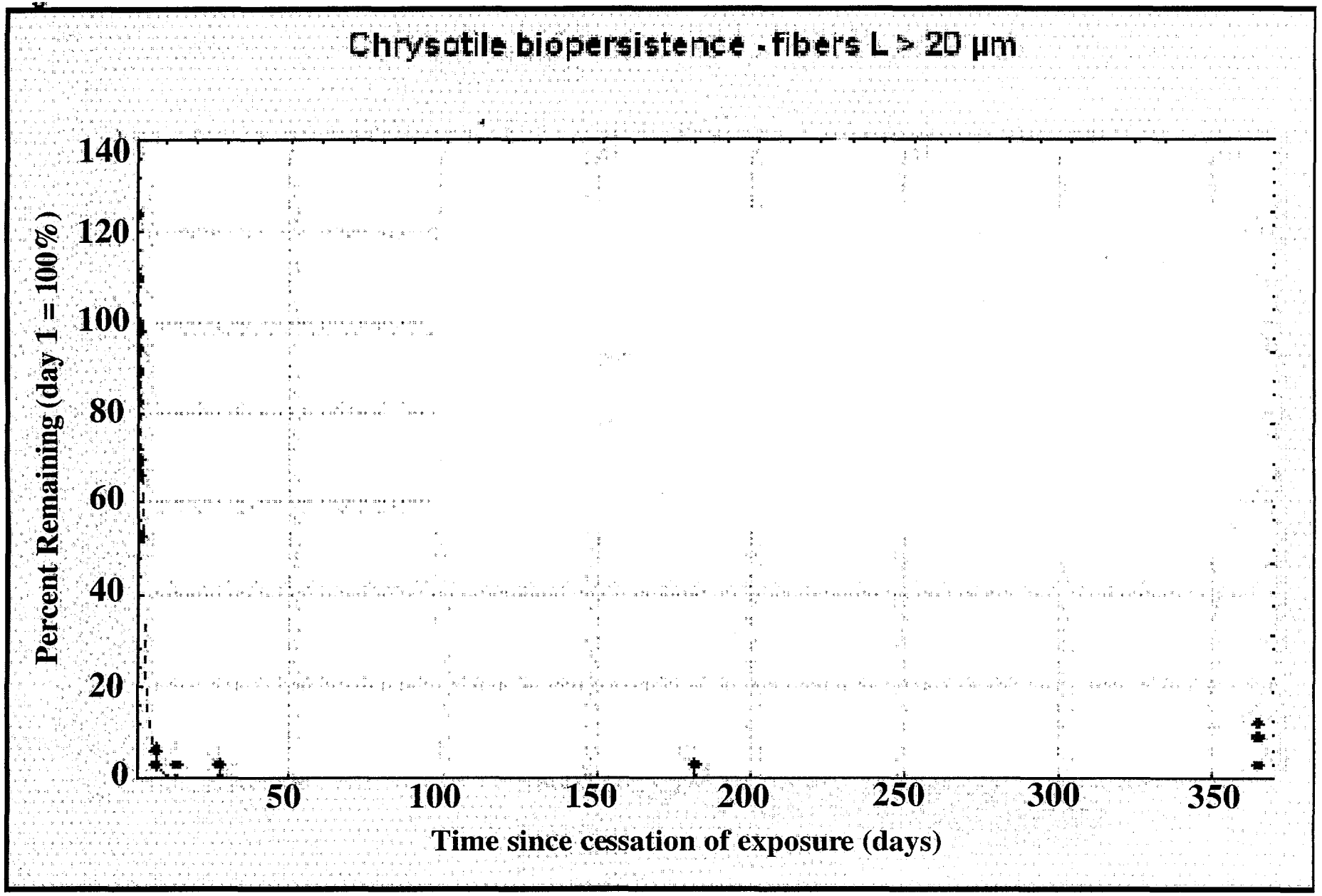
Asbestos Type*	Fibrosis	Lung Tumors	Mesothelioma	T1/2, days
Amosite	+	+	+	>1000
Crocidolite	+	+	+	~1000
Tremolite	+	+	+	like other amphiboles(?)
Anthophyllite	+	+	+	1000 (?)
Chrysotile	+	+	+/–	~2 – 140

Note:* ***All asbestos types induced mesothelioma in rats following intracavitary injection (pleural, peritoneal) of very high doses (1×10^7 - 1×10^9 fibers, equivalent to a lung dose greater than the weight of the lung)*

Biopersistence and Effects of Chrysotile in Rats

Study	Fiber Characteristics	Biopersistence	Interstitial Fibrosis	Lung Tumors	Pleural Mesothelioma
Wagner *et al.*, 74 **10 mg/m^3, 24 mos**	**Rhodesian** **Canadian**	Steady-state lung burden, no build-up	+ +	+ +	– +
NTP, 78/79 *(McConnell et al., 82 Pinkerton et al., 82/84 Ilgren & Chatfield, 97/98)* **~8-11 mg/m^3, 12 mos**	**UICC-B** **Long** *(Jeffrey,Quebec)* **Short***(Coalinga, CA)*	**Not done** *(Si-content variable + inconclusive)*	+ + –	+ + –	– – –
Platek *et al.*, 85 **1 mg/m^3, 18 mos**	**Chrysotile, short** (JM)	**40% clearance** <5 µm *(6 mo post-expos.)* **no clearance** >5 µm *(6 mo post-expos.)*	–	–	–
Muhle *et al.*, 87 **6 mg/m^3, 12 mos**	**Coalinga** *(short)*	**90% clearance** *within 10 mos*	(+)	–	–
Davis & Jones, 88 **10 mg/m^3, 12 mos**	**"Short" Canadian** **Long**	**90% clearance** *(6 mos post-expos)* **50% clearance** *(6 mos post-expos)*	(+) +	+ +	– +
McConnell *et al.*, 91 **10 mg/m^3, 12 mos**	**Jeffrey** *(Quebec)*	**not done**	+	+	–
Bernstein *et al.*, 99;00	**Brazilian** *(Cana Brava)* **(465 f/cm^3 >20 µm)**	**T1/2=1.3 d** >20 µm **T1/2=2.4 d** >5-20 µm	**Abstracts Only**	***Results Not Yet Published***	

Bernstein *et al.*, 2000



ENVIRONMENTAL FACTORS

MIXED DUST EXPOSURES: POTENTIATION OF FIBER EFFECT?

Macrophage function may be affected in additive/synergistic fashion:

— **clearance function** *(Ferin and Leach, 1976)*

— **greater accumulation of fibers** *(e.g., smoke + crocid., Muhle et al., 1989; smoke + amosite, Churg et al., 1992)*

— **phagolysosomal dissolution affected?**

— **increased long-term effects**

- **amosite or chrysotile ± SiO_2 or TiO_2** *(Davis et al., 1991)*
- **brucite** (9 mg/m^3) **+ chrysotile** (1 mg/m^3, contaminant) *(Davis et al., 1985)*

Mixed Dust Exposures in Rats *(Davis et al., 1991)*

Chrysotile or amosite (10 mg/m^3) plus TiO_2 (10 mg/m^3) or quartz (2 mg/m^3), 1-year rat inhalation study plus 2-year observation period

	Fiber retention	Pulm. fibrosis	Transport across visc. pleura	Lung tumors	Mesothelioma	Survival rate
Chrysotile + TiO_2	↑	○	?	↑	↑[a]	↑
Amosite + TiO_2	○	○	↑	↑	↑	↑
Chrysotile + quartz	↓	↑	?	↑	↑[a,b]	↓
Amosite + quartz	○	↑	↑	↑	↑[b]	↓

○ *no change;* ↑ *increased;* ↓ *decreased; (compared to asbestos alone)*

*(predicted lung burden of TiO_2 in "**overload**" range, ~10 mg/lung)*

[a] = *no mesothelioma with chrysotile alone*

[b] = *greater effect of added quartz than of added TiO_2*

Host Factors for Increased Susceptibility to Asbestos

Compromised respiratory system:

- **Synergism smoking and occupational exposures ⟶ fibrosis, lung tumors**

Diet:

- **Lower incidence of asbestos induced lung tumors ⟶ dietary restriction study, mice**
  (Koizumi et al., 1993)

Genetic deficiency:

- **GST-mu and NAT deficiency ⟶ associated with increased susceptibility**
  (Smith, 1994; Hirvonen et al., 1996; Saarikoski et al., 1997)

Experience from PM Studies

(non-carcinogenic effects)

Association between ambient PM levels and increased morbidity/mortality from respiratory/cardiovascular disease in compromised people.

But: *No data for ambient asbestos exposures*

CONCLUSIONS
— Concepts of Asbestos Toxicity —

- **Dimension and Biopersistence** ⟶ **most important determinants of toxicity**
  - — **clearance of short *vs.* long fibers** *(AM-mediated vs. epith. cells, translocation)*
  - — **long** *(>20 μm)* **and thin** *(~0.5 μm)* ⟶ **more carcinogenic than short fibers**

    ***but:* short fibers contribute to risk** *(do not disregard fibers < 5μm, especially if clearance is retarded)*
  - — **amphiboles** ⟶ **high biopersistence**
  - — **chrysotile** ⟶ **lower biopersistence, difference between localities?**
- **Dose and Dosemetric:**
  - — **respirability** *(aerodynamic behavior)*
  - — **fiber number** ⟶ **cancer dosemetric**
  - — **fiber surface area** ⟶ **non-cancer endpoints?**

CONCLUSIONS (Con't)
— Concepts of Asbestos Toxicity —

- **Rat inhalation studies:** amphiboles ⟶ fibrosis, lung tumors, mesothelioma
  chrysotile ⟶ range of responses: locality, contaminants?

- **Mixed dust exposures** *(asbestos + particles)* ⟶ increased fibrogenic, tumorigenic effects

- **Host factors** *(pre-existing conditions)* ⟶ increased susceptibility

ASSESSING ASBESTOS-RELATED RISK: EVALUATING ENVIRONMENTAL EXPOSURES WHEN BUDGETS AND RESOURCES ARE LIMITED

DW Berman*, *Aeolus, Inc., Albany,-CA*

To support risk management decisions concerning an identifiable source of asbestos, the risk that is uniquely attributable to that source needs to be evaluated. This requires both that contributions to airborne exposure from the source be distinguished from the contributions of other sources (i.e. background) and that long-term exposure be adequately characterized.

Measurement of airborne asbestos concentrations with adequate sensitivity to detect asbestos over the full range of interest for risk assessment is expensive. Moreover, due to the inherent variability of environmental conditions (including meteorology and source characteristics), the number of measurements typically required to distinguish source contributions from background and to properly characterize long-term exposure can be prohibitively large in many cases.

This poster presents an alternate approach for assessing exposure and risk that involves use of a method for measuring asbestos in soils and bulk materials and coupling such measurements with published dust emission and dispersion models that are selected to match conditions at a site. The "Modified Elutriator Method for the Determination of Asbestos in Soils and Bulk Materials" is unique among asbestos methods because it provides the kind of results that can be combined with published dust emission and dispersion models to predict downwind asbestos exposures with reasonable accuracy and precision. Results of studies demonstrating the utility of the approach and of its application to support two recent risk assessments are presented.

ASSESSING ASBESTOS-RELATED RISK: NEW THINKING/ NEW PROTOCOL

DW Berman*, *Aeolus, Inc., Albany, CA,*
KS Crump, *The KS Crump Group, Inc., Ruston, LA*

To assess risk, it is typically necessary to combine an exposure estimate from an environment of interest with a dose-response coefficient derived from an unrelated environment using a model (and dose-response coefficient) that is appropriate for the disease end point of interest. Unfortunately, the dose-response coefficients that have been published for asbestos vary by more than a factor of 500 for lung cancer and more than a factor of 1000 for mesothelioma, the two disease end points of principal concern for environmental asbestos exposures. Given this apparent variation, the validity of applying these coefficients to predict risk must be given due consideration.

The observed disparity in published dose-response coefficients for asbestos has been variously attributed to differing mineralogy (which affects surface chemistry and biopersistence), differing fiber size and shape, and (in a few cases) special exposure circumstances that are unique to a particular environment. The traditional approach for measuring asbestos is not sensitive to these distinctions so that their effects potentially contribute to the observed variation in dose-response coefficients. Moreover, the dose-response coefficients traditionally recommended for asbestos are single values (one each for lung cancer and mesothelioma) selected within the ranges reported among the published studies without regard to the effects of mineralogy, fiber size and shape, or the need to consider cross-study predictability.

This poster presents an alternate approach for assessing asbestos-related risk that incorporates improved methods for characterizing asbestos exposure concentrations combined with identification of an adjusted set of dose-response coefficients that better reflect the effects of mineralogy and fiber size and shape. An evaluation of cross-study predictability is also presented along with consideration of the potential magnitude of the error in the risk estimates that are derived using this new approach.

THE BIOPERSITENCE AND BIOACCUMULATION OF AMPHIBOLE ASBESTOS AND VITREOUS FIBERS.

R. C. Brown[1] and J. Turim[2], [1]*Toxicology Services, Uppingham, UK* [2]*Sciences International. Inc., Alexandria, VA*

Interest in the ability of toxic materials to persist in the body is widespread with a group of persistent bioaccumulative toxic (PBT) materials receiving special attention. This group includes amphibole asbestos, which can accumulate in the lung to a greater level than other fibres and persists longer after exposure ceases. This has been known since Wagner[1] demonstrated that crocidolite followed this pattern and further evidence is provided by the fact that amphiboles are the most common fibre type in the lungs of persons exposed to mixtures containing predominantly chrysotile.

The use of biopersistence as a regulatory tool in the European Union classification of man-made vitreous fibres[2] is an outgrowth of research into this phenomenon carried our over the last ten years. Biopersistence is clearly related to chemical composition but the preferential phagocytosis of short fibres exposes long and short fibres to different environments. Hence they may dissolve through different mechanisms. There is strong evidence that fibres greater than 20 μm long are most responsible for pathogenesis and this provides part of the justification for the concentration on long fibres in the EU classification. However shorter fibres must have some pathogenic activity and therefore it is difficult to justify using any one measure to summarise fibre clearance. However we suggest that long fibre clearance is a consistent, relevant and reproducible measure related to risk.

For relatively insoluble fibres such as e-glass and amphibole asbestos the clearance of long and short fibres was similar but for more soluble fibres, such as most man made silicate wools, long fibres cleared preferentially. The different roles of solubility and cell-mediated clearance could be distinguished by differences in the accumulation and persistence of amphibole asbestos, glass fibres, and glass particles. The clearance of glass fibres continued even under conditions where macrophage mediated clearance has collapsed due to pulmonary overload.

Short fibre clearance is largely unaffected by particle properties, these fibres are phagocytosed by macrophages and, whether soluble in that compartment or not, they are cleared from the lung unless prevented by very high lung burdens unlikely to occur in man. The pool of short fibres is also influenced by the corrosion, and transverse breakage of long fibres. Therefore being the result of several processes, the clearance of short fibres is complex and, perhaps, less directly related to the conditions after human exposure. This does not rule out, however, the possibility that some short fibres, even if soluble under extracellular conditions, will be toxic to macrophages and accumulate to dangerous concentrations especially as their number may be enhanced by fragments of longer fibres. Despite the possible contributions of short fibres to pathogenicity, overall the clearance of long fibres is a biologically relevant measure directly related to the fibre's material properties and predictive of biological effect.

These considerations have identified considerable gaps in our knowledge on the biopersistence, bioaccumulation and toxic properties of chrysotile asbestos.

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[1] Quoted in IARC Monograph Volume 14 – Asbestos WHO International Agency for Research on Cancer Lyon 1977

[2] EU directive 97/69/EC 1997

A Pilot Project to Map Areas Likely to Contain Natural Occurrences of Asbestos—El Dorado County, California

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Chrysotile and tremolite asbestos occur naturally in California, most commonly in areas of ultramafic rock and serpentinite. Maps identifying these areas are necessary to establish policies and regulations that protect the public from asbestos exposure. Available geologic maps identify most locations of ultramafic rock and serpentinite, but are generally too technical for health agencies, environmental agencies and the public to use. Often, no single map shows all known ultramafic rock and serpentinite occurrences in a given area. These shortcomings led the Department of Conservation, Division of Mines and Geology (DMG) to undertake a pilot project to develop an easily understood map showing areas geologically favorable for asbestos in El Dorado County. This county was chosen for mapping because of current public concerns about exposure to asbestos in dust generated during construction and mining activities.

The project map was compiled from 26 existing geologic and soils maps and field checked for accuracy. Information about asbestos and proper map use, written for non-geologists, was included on the map. Satellite imagery of the county was evaluated for its usefulness in locating ultramafic rock and serpentinite areas. It proved useful where vegetation or cultural development did not obscure rock exposures.

A 10-person panel reviewed the map and accompanying report. Members were from outside DMG and had expertise in serpentinite and asbestos mineralogy, California geology, soils and land-use planning. Before public release, appropriate government agencies and the press were briefed about the map and its proper use. Digital versions of the map and report were placed on the DMG website and paper copies were distributed to El Dorado County to allow immediate viewing upon map release. The panel review, briefings, website and paper copy availability, and design of the map for non-geologists contributed significantly to acceptance of the map with minimal public apprehension.

ASBESTOS IN NATURAL OUTCROPS OF SERPENTINE

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There is no scientific consensus regarding health risks of exposure to asbestos at low levels found in the air around natural serpentine rock. In the San Francisco Bay area there are significant tracts of naturally occurring asbestos-bearing serpentine. These tracts are present in residential areas, recreational parks, underlay school yards or reservoirs and occupy significant tracts of land under control of local, state, and federal governments. It is unknown if there is a real health risk from exposure to asbestos fibers at the low levels found in these serpentine tracts. There has been no systematic evaluation of the health risks related to exposure of asbestos fibers released from these naturally occurring serpentine tracts in the San Francisco Bay Area. To characterize these serpentine tracts systematic geologic mapping should be done at a scale useful for realistic site assessment. Grid sampling of the serpentine mapped areas should be used to establish distribution and concentrations of the asbestos mineral species in rock, soils and water. Laboratory analyses would identify the asbestos mineral species along with estimates of fibers that might be released by crushing or pulverization. Stationary or personal air monitors can be used to guesstimate the amount of asbestos fiber in the air mass above the serpentine rock during construction (excavation). There is no medical or statistical consensus regarding a safe threshold for asbestos fibers at low levels or intermittent exposure around natural or disturbed serpentine. Realistic risk assessments are still needed that utilize new mineralogical, geological, and epidemiological data. Those San Francisco Bay cities and/or counties that have significant exposures of serpentine need to survey its extent and establish prudent laws for serpentine land development.

EXPOSURE TO TREMOLITE FIBERS OF NATURAL ORIGIN IN EL DORADO COUNTY, CALIFORNIA

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In this paper we describe our studies of the El Dorado, California, naturally occurring tremolite asbestos. In the process of doing a day's fieldwork, with minimal visible dust, one of the authors (MG), a geologist and physician, documented his exposure to tremolite fibers. These fibers were recovered in purulent sputum the next morning in the setting of a brief and mild dust-induced bronchitis. A laryngeal washing of 400 cc, taken 3 months later, showed retained tremolite fibers in the process of oxidation and splitting, with a fiber concentration too high to measure without diluting the sample. The tremolite in samples from several field sites was analyzed by PLM, SEM, TEM, and SEM electron microprobe of polished sections. Sputum and washings were analyzed by PLM and by SEM and TEM, respectively. Crystallographic data indicate an oxidation/cleavage mechanism of fine fiber formation, resulting from progressive splitting along cleavage traces in massive to coarsely fibrous tremolite. High resolution TEM showed continuous double chains between conjoined fibers prior to splitting. In weathered samples, retained fiber, and fiber produced by hydrogen peroxide oxidation of crushed, optically continuous, fresh samples, longitudinal fiber surfaces were eroded irregularly by oxidation, cutting across cleavage planes and producing an amorphous oxidation product that sometimes clung to fiber surfaces. Oxidized fibers are highly electrostatic, linking in chains in undercoated environmental surfaces, and in "snowflakes" that periodically fall and cover residential dwellings after a light summer rain on hot, dry, tremolite-laden soil. Fiberization, emergence of flexiblility, and spontaneous inter-fiber rotation were observed with progressive fiber splitting. The oxidized tremolite is itself highly oxidizing, suggesting mechanisms for induction of purulent response and oxidative carcinogenesis. TEM and HRTEM data are presented comparing tremolite samples from this locality with tremolite known to be carcinogenic in human epidemiological and experimental animal studies. Together, all these data indicate a potential risk of substantial exposure and consequent health risks from this naturally occurring asbestos for the population of the area. Of special concern are even low level exposures to infants and children as a result of development and subsequent disturbance of the exposed tremolite.

WINCHITE AND COCIDOLITE ABESTOS IN A HISTORICAL SAMPLE OF THE LIBBY, MONTANA VERMICULITE PRODUCT

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A historical sample of the crushed and expanded vermiculite product from the former W.R. Grace and Company mine in Libby, Montana was obtained and analyzed. The product was mined from a weathered biotite pyroxenite consisting mostly of clinopyroxene, vermiculite, and biotite. Examination with a 10X hand lens revealed no asbestiform amphiboles. Under polarized light microscopy at magnifications of 100X to 1500X, dust from the sample was found to contain about 18% fibrous amphibole. The amphibole had a distinct blue or blue-green to yellow or yellow-brown pleochroism, with some deeper blue lamellae consistent with magnesioriebeckite. All optical data were consistent with identification as of the amphiboles as winchite with trace crocidolite. Fiber and fiber aggregates were in various stages of progressive near-surface weathering alteration. Fresh fibers were coarse and blocky, with sharp, inclined extinction. Alteration caused oxidation and splitting along cleavage planes, producing shredded and oxidized aggregates of shard-like fibers and thin fibers of high aspect ratio, along with an amorphous oxidation product. Quantitative TEM analyses of fibers of the suspended dust were performed using electron diffraction and X-ray spectroscopy on randomly selected amphibole fibers. Spectroscopic chemical analyses used established mineral standards and were fully corrected for variables that could cause errors in the analyses. Four shard-like fibers, with a mean aspect ratio of 7:1, were found to be winchite. Two long (greater than 15 microns), high aspect-ratio fibers were of indistinguishable winchite composition, while one was of magnesioriebeckite or crocidolite composition. Semi-quantitative data on numerous other fibers showed all to be consistent with quantitative data. Previously, two gross asbestos samples from Libby have been reported (1) to be winchite, but we know of no previous reports of winchite or crocidolite in the product. Others have reported gross samples and microscopic fibers to be of tremolite, actinolite, and/or richterite composition. None of these other minerals were found by TEM. Winchite is currently unregulated under OSHA and EPA. Amphibole fibers formed by splitting rather than crystal faces are also unregulated under OSHA and under dispute in current EPA practice. The importance of fiber surface oxidation is not considered, despite the clear role of oxidation products in carcinogenesis. Further quantitative mineralogical analyses are urgently needed, including analyses of fibers recovered from tissues of exposed individuals.

1. Wylie, A., and Vertrouteren, J. (2000) American Mineralogist 85, 1540-1542.

EVALUATION AND REMEDIATION OF RESIDENTIAL ASBESTOS CONTAMINATION FROM A VERMICULITE EXFOLIATION FACILITY IN MINNEAPOLIS, MN.

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The Western Minerals site in NE Minneapolis was a vermiculite exfoliation facility that operated from approximately 1937 until 1989, during which it has been estimated to have processed as much as 118,465 tons of vermiculite ore from the Libby, MT mine. During the peak periods of operation (1950s-1970s), the plant operated 24 hrs per day. The unexfoliated material from the vermiculite exfoliation processing, referred to as stoner rock, was disposed of in large piles outside the loading dock. The material was made available to the general public as "free crushed rock", and members of the local community brought the material to their residences for use as fill material for driveways and yards. Visible tremolite asbestos bundles are scattered throughout the area where the former piles of stoner rock were located. EPA sampling of the former pile area showed concentrations up to 20% asbestos. Asbestos was frequently detected in surface soil throughout the property, ranging up to 8%. Electron microscopic analysis revealed the fibers were amphibole asbestos, with numerous fibers greater than 10 microns and aspect ratios > 10. Residences where stoner rock was known to have been taken showed large, visible bundles of asbestos, confirmed by lab analysis as tremolite asbestos. Since September, 2000, EPA has been engaged in the remediation of 22 residential properties contaminated with asbestos from the stoner rock material. At least 25 additional properties are scheduled for remediation this spring and more properties are expected to be identified from future inspection. EPA and the MN Dept. of Health (MDH) have received many reports of asbestos-related disease in residents who have lived in the predominantly residential area surrounding the facility. An ATSDR-funded survey is being conducted by MDH to determine the magnitude of the impact on both residential and occupational exposure to asbestos from this facility.

COMPARISON OF ENVIRONMENTAL AND OCCUPATIONAL EXPOSURE TO CROCIDOLITE AND THE INCIDENCE OF MESOTHELIOMA.

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Introduction—Crocidolite (blue asbestos) was mined and milled at Wittenoom by the Australian Blue Asbestos Company from 1943 to 1966. Because of the remoteness of the operations, many workers were accompanied by their families who were exposed to crocidolite in and out of their homes. The cohorts of nearly 7000 workers and 5000 residents have now been followed up to December 1999.

Methods—Work and environmental histories, follow-up and crocidolite exposure were estimated as previously described. Additional follow-up was done through the Australian National Death Index and Cancer Clearing House, as well as through Italian social security records. Exposure effects were estimated using Cox regression for mesothelioma, lung cancer and all cause mortality.

Results—There were 192 cases of mesothelioma in the workers group and 47 among the residents who all had valid data. Mesothelioma mortality increased 64% (95% CI 48-81%) per log day of exposure and 43% (95% CI 25-65%) per log fibre/ml of exposure and was 40% lower in women than in men. There were no significant differences in exposure-response relationships between the 2 cohorts, although after allowance for time after first exposure, the relative risk increased with age at first exposure.

Conclusion—Further follow-up on these two cohorts exposed exclusively to crocidolite has shown a continued increase in mesothelioma occurrence with no difference between the two types of exposure after control for duration and intensity.

CONCORDANCE OF RAT AND HUMAN DATA-BASED RISK ESTIMATES FOR LUNG CANCER FROM CHRYSOTILE ASBESTOS

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Introduction: Risk assessment often relies on animal bioassay data to predict risks in humans, requiring extrapolation from animals to humans and usually from higher animal doses to lower human doses. Few human exposure-response data are available for assessing the validity of these assumptions. In this study, we use existing data in both rodents and humans to quantitatively compare the exposure, dose, and response relationships in humans and animals.

Methods: In the first phase of this study, we used a quantal multistage model to compute the toxic doses (TDs) associated with a 0.01, 0.1, 1, and 10% excess risk of lung cancer in two studies of male rats (Wistar-derived strain AF/HAN; inhalation exposure, 2 and 10 mg/m3, 7 hr/day, 5 day/week, 12 months, killed at approx. 30 months). The rat-based TDs were extrapolated to humans using allometric and lung surface area scaling approaches. Human-based TDs were derived from three human studies (two of Canadian miners/millers and one of U.S. textile workers), using Poisson regression modeling and lifetable analyses. Ratios of the rat- and human-based TDs were computed to evaluate concordance of the risk estimates.

Results: The TD ratios from the studies in rats and Canadian miners/millers varied from 0.3 to 3 for the scaling approaches of body surface area, metabolic rate, and air intake; while the TD ratios for body weight and lung surface area were more variable (1.5 to 20). The TD ratios comparing rats to the textile workers were all higher, ranging from approximately 20 to 800. Overall, the rat-based risk estimates for lung cancer in humans were reasonably concordant to those from the Canadian miners/millers studies, suggesting similar sensitivity in rats and humans. In contrast, the risk estimates were much higher from the textile workers study, suggesting humans are more sensitive. It is unknown how the airborne fiber size distributions compared between the rat studies and either human study; however, there is some evidence that the textile workers may have been exposed to longer fibers than the Canadian cohorts.

Discussion: The next phase of this study includes the development of lung dosimetry models, using existing data in rodents, cynomolgus monkeys, and humans, to compare the kinetics of chrysotile clearance and retention across species. Exposure, dose, and response relationships will be examined for both neoplastic and nonneoplastic lung responses, using statistical and biologically-based models. Fiber dimension will be investigated as a potential factor in lung fiber retention and response. The kinetic and mechanistic findings from this study may be especially useful for extrapolating from animal bioassay data to predict disease risk in humans exposed to airborne fibers.

ENVIRONMENTAL EXPOSURE TO TREMOLITE AND RESPIRATORY CANCER IN NEW CALEDONIA (SOUTH PACIFIC)

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A case-control study on respiratory cancers was conducted in New Caledonia, where a high incidence of malignant pleural mesothelioma had been observed. The disease pattern suggested an environmental exposure to asbestos. The first results showed that, in some areas, tremolite asbestos derived from local outcroppings has been used as a whitewash (locally named "pö") for indoor and outdoor walls of the houses. All cases diagnosed between 1993 and 1995 (including 15 pleural mesotheliomas, 228 lung cancers and 23 laryngeal cancers) and 305 population controls were included in the study. Information on past or present use of the whitewash, residential history, smoking and occupation was collected. In addition, biologic samples (lung tissue or liquid from bronchoalveolar lavage) and airborne samples were collected and analyzed by analytical transmission electron microscopy.

The risk of mesothelioma was strongly associated with the use of the whitewash (OR=40.9; 95% CI=5.15-325). Among Melanesian women, exposure to the whitewash was associated with an increased risk of lung cancer (OR=4.89,CI 1.13-21.2). In contrast, no association was noted between exposure to pö and lung cancer risk among Melanesian men, probably because of lower exposure levels.
The analysis of biologic samples showed that the lung burden of tremolite fibers was strongly associated with the use of pö.

The highest airborne tremolite concentrations were reached during sweeping inside whitewashed houses (420 to 3900 f/l). Tremolite fibers at lower concentrations were also observed in whitewashed houses during a normal activity (up to 150 f/l) and in outdoor samples collected near whitewashed houses (up to 25 f/l). Moreover, results of a descriptive survey have shown that women spend on average about 2 hours more per day indoors than men do. These results support the hypothesis of a higher lifetime exposure to tremolite for women.

THE CHEMICAL COMPOSITION AND PHYSICAL PROPERTIES OF AMPHIBOLE FROM LIBBY, MONTANA: A PROGRESS REPORT.

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Research into the current health crisis in Libby, Montana is providing information indicating that the ten to thirty year-old definitions, analytical procedures, and regulations pertaining to health risks from asbestiform minerals may not be adequate. The USGS is currently characterizing a representative suite of thirty amphibole samples obtained from the site of former vermiculite mining operations near Libby. We have identified a continuous range of amphibole compositions, which by current nomenclature, cause the minerals to be classified as winchite, richterite, tremolite, actinolite, ferro-edenite and magnesio-arfvedsonite. Because these phases (except tremolite and actinolite) are not among the six types of asbestos cited in current regulations, their potential links to the extensive health problems at Libby suggest that the mineralogical definitions currently used to regulate asbestos may be in need of further refinement. We are also examining the mineralogical and geochemical significance of the morphological term "asbestos fiber" with respect to potential toxicity. We have identified, in most of the Libby area amphiboles, a variety of morphologies including asbestiform fibers, acicular cleavage fragments, acicular partings, and blocky, non-fibrous crystals. The role of the acicular cleavage fragments and partings in the toxicity of the Libby area amphiboles is uncertain but clearly in need of detailed study. Of particular concern is the distinction currently made between asbestos fibers and acicular cleavage fragments, with the acicular cleavage fragments often viewed as non-regulated. We are currently evaluating whether this distinction is applicable to the Libby area amphibole and is warranted from a mineralogical, geochemical, and hence toxicological perspective. Information gained from this project will be coupled with toxicological studies to enhance the current state of knowledge about acicular amphibole of varying chemistry, and to provide a foundation for reexamination of current definitions and analytical procedures.

ENVIRONMENTAL ASBESTOS AND INCIDENT MESOTHELIOMA IN CALIFORNIA

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Objective: To examine the relation between mesothelioma incidence and environmental asbestos in Calif. during the period 1988-97.

Methods: Ecological study at county and census tract level using GIS approaches. Analysis of 2949 incident mesothelioma cases and the digital map of ultramafic rocks in Calif. that are the principal source of asbestos in the environment.

Results: Exact residential addresses at diagnosis were available for 93% of cases and matched to a unique intersection. 7% of cases were matched to a 5-digit zip vicinity. Mesothelioma cases were geocoded on the Calif. state map and assigned to census tracts. Most cases were located in cities near the West Coast or along rivers in Calif., most likely reflecting occupational asbestos exposure. Population-weighted correlation analysis (1990 population) showed mesothelioma incidences are significantly correlated with asbestosis mortality ($P<0.0001$) and population-weighted distance to the nearest asbestos deposits ($P=0.0016$) at county level. GIS buffer analysis showed the ten-year age-adjusted mesothelioma incidence aged 35+ (12.5 per 100,000) in asbestos deposit areas was not significantly higher than those in their buffers. Mesothelioma incidences within 3,4,5,6,7, and 8 km buffers were 16.4, 15.5, 17.6, 17.6, 16.7, and 18.9 per 100,000 respectively, significantly higher than the incidence (12.7 per 100,000) in Calif. There was no evidence of a dose-response between mesothelioma incidence and the distances from asbestos deposits and their buffers. Similar results were observed when counties with a higher mesothelioma incidence were excluded.

Conclusion: Occupational exposure to asbestos is a dominant determinant for occurrence of mesothelioma in Calif.. The relation between environmental asbestos and mesothelioma must be assessed based on more detailed exposure information such as individual histories of occupational exposure and residence for cases.

MAPPING OCCURRENCES OF POTENTIALLY ASBESTOS-BEARING SERPENTINITES AND TREMOLITIC ROCKS IN THE SIERRA NEVADA FOOTHILLS OF CALIFORNIA USING IMAGING SPECTROSCOPY

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Imaging spectroscopy data collected by the Airborne Visible/Infrared Imaging Spectrometer (AVIRIS) during the summer of 1997 over portions of Calavaras County in foothills of the Sierra Nevada of California have been mapped using the USGS Tetracorder spectral mapping algorithm. Resulting mineral maps of the 2 - 2.5 micron reflectance spectral region reveal numerous outcrops of chrysotile- and antigorite-bearing serpentinite and several outcrops of tremolite/talc- bearing schists along a major fault zone. Surface mineralogy of the serpentine bodies is detectable with AVIRIS in some cases because of the low density vegetation cover associated with the high Mg soils developed on these rocks. In cases where the vegetative cover is too thick to directly map surface mineralogy, it may be possible to indirectly map serpentinites and ultramafic rocks based on their close association with chaparral vegetation. Spectral detection of tremolite/talc-bearing units was limited to well exposed rocks in quarries and along shorelines. Tetracorder was able to map different grain sizes of chrysotile in rocks exposed in an asbestos quarry. With additional work it may be possible to correlate chrysotile grain size with degree of fibrous crystal habit. A small portable field spectrometer has been successfully used to detect serpentine minerals in hand specimens. The correlation between spectral detection of serpentine minerals and presence of protocol asbestos fibers will be explored as a possible technique to screen samples in the field allowing those with high potential to be selected for more in depth analysis. Such a screening tool could accelerate the process of mapping entire counties for asbestos potential at the hand specimen or remote sensing scales.

RISK OF LUNG CANCER FROM EXPOSURE TO VARIOUS FIBERS

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The relative toxicity of different types of asbestos and other mineral fibers has been the subject of great debate. Toxicity Equivalency Factors have been used by the US EPA and other agencies to represent the risks of individual agents within a class relative to a representative member. By taking into account differences in biopersistence, and assuming that all lung resident fibers have identical potencies, we use such an approach to characterize the risk of lung cancer, relative to amphiboles, from chrysotile asbestos and man-made vitreous fibers.

We used a deposition clearance model to generate time-dependent lung burdens in rats of a dozen long fibers for various exposure concentrations. Together with a previously estimated potency factor for long fibers[1,2], we used the generated lung burdens to estimate risks of lung cancer in rats associated with inhaled fibers. Over a broad range of exposure concentrations, excess risk is a linear function of exposure concentration for aerosols with equal deposition efficiencies. Excess lung cancer risk is also a linear function of weighted half-life for fibers for which the weighted half-life is short compared to the life span of the rat. When the weighted half-life is long, as in the case of amosite asbestos, the relationship departs from linearity because the lung burden does not reach equilibrium in a rat's lifetime.

We explore whether these concepts can be used to rank, for different types of fibers, the excess risk from occupational exposure through inhalation. Since even fibers that have long half-lives reach equilibrium relatively early in a human lifetime, one would expect to observe approximate linearity between the weighted half life and excess risk. This observation suggests that human lung cancer risk associated with different inhaled fibers can be compared using the results of the short-term experiments that are conducted to determine weighted half-life.

[1] Moolgavkar SH, Luebeck EG, Turim J, and Brown RC. Lung cancer risk associated with exposure to man-made fibers. *Drug and Chem Tox*, 231(1), 223-242 (2000).
[2] Moolgavkar SH, Turim J, Brown RC, and Luebeck EG. Long man-made fibers and lung cancer risk. *Reg Tox and Pharm (in press).*

IDENTIFICATION OF TREMOLITE-ACTINOLITE ASBESTOS

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Tremolite and actinolite asbestos form part of a solid solution series defined by the ideal composition $Ca_2 (Mg,Fe)_5Si_8O_{22}(OH)_2$. Other chemical substitutions can occur that introduce variable amounts of Na, Al, Mn, Cr, Ti, F, and K, for which maximum atomic proportions are specified by nomenclature convention. The physical properties used to identify the amphibole, including optical properties (e.g. refractive index) and the dimensions of the unit cell (obtained by diffraction methods), are dependent upon composition. A large-scale study designed to place statistical limits on the range in values for these properties in the tremolite-ferroactinolite series was undertaken and reported by the authors[1]. Two of the samples from this study are being prepared for reissue as part of a NIST standard reference material (SRM 1867a) for uncommon commercial asbestos that includes tremolite, actinolite, and anthophyllite asbestos. One half of the 35 asbestiform samples analyzed in [1] contain some fibers that have optical properties that are consistent with massive tremolites and actinolites. The remaining samples present only anomalous optical properties, similar to those of crocidolite and amosite, that include parallel, rather than inclined, extinction, and changes in refractive indices. These anomalous properties will be described. In addition, the properties of the asbestiform amphibole from the vermiculite mine in Libby, Montana[2], will be described.

[1]J.R. Verkouteren and A.G. Wylie (2000) American Mineralogist 85, 1239-1254.
[2]A.G. Wylie and J.R. Verkouteren (2000) American Mineralogist 85, 1540-1542.

ASSESSMENT OF OCCUPATIONAL AND RESIDENTIAL EXPOSURES TO ASBESTOS IN SOIL

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Situation—Abandoned Power Plant in a residential Boston neighborhood – on the Boston Harbor. Probable release of asbestos to air and soils surrounding power plant building. Possible release mechanisms include damaged asbestos containing materials on exterior piping and damaged asbestos-containing materials on interior piping exposed to the weather due to building damage and vandalism.

Issues—How to remediate the site and demolish the building without releasing asbestos into the air in concentrations at levels that would present risks to workers at the site, neighboring residents living close to the site, and local residents who pass by the site on their way to their fishing boats moored at the adjacent docks.

Solution—Establish asbestos action levels for air, dust and soil based on inhalation of fugitive dust to protect workers and residents during remedial activities. Monitor air and dust during the work to keep the concentrations of dust/asbestos below the action levels. Characterize risk of potential exposures to remediation workers, local resident trespassers and local residents during expected periods of remediation. Use measured asbestos concentrations in soil and measured dust concentrations to characterize risk.

ASBESTOS-RELATED DISEASES FROM ENVIRONMENTAL EXPOSURE TO CROCIDOLITE IN DA-YAO, CHINA I. REVIEW OF EPIDEMIOLOGICAL & COHORT DATA

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Objectives—Scattered patches of crocidolite, one form of asbestos, were found in the surface soil in the rural county of Da-yao in southwestern China. In 1983, researchers from the West China University of Medical Sciences (WCUMS) discovered that residents of two villages in Da-yao had pleural plaque and pleural mesothelioma that had reached the proportion of hyper-endemic state. More studies have been conducted to unveil the severity of the health impact. The purpose of this paper is to review and summarize these studies, along with other relevant data, and to discuss the potential contribution to environmental risk assessment.

Method—This report is based on a review of several clinical/epidemiological studies conducted by WCUMS researchers since 1984, which included one cross-sectional medical examination survey, one clinical/pathologic analysis of 46 cases of mesothelioma, and three retrospective cohort mortality studies. Additional information acquired from reviewing original data first hand during a personal visit along with an interview of investigators and medical specialists from Da-yao County Hospital was also incorporated.

Results—The prevalence of pleural plaque was 20% among peasants over 40 years of age in the Da-Yao villages in the cross-sectional survey, a reflection of significant asbestos exposure in the past. The average number of mesothelioma cases was 6.6 per year in the 1984-1995 period and 22 per year in the 1996-1999 period, a clear trend of an increase with time. For those mesothelioma cases that were histology-confirmed, there were 3.8 cases/year in the first period and 9 cases/year in the second, in a population of 68,000. Of the 2,175 peasants in this survey, 16 had asbestosis. In the cohort studies, lung cancer deaths were significantly elevated in all three-cohort studies. The annual mortality rate for mesothelioma was 85 per million, 178 per million, and 365 per million for the three cohort studies, respectively. The higher exposed peasants by living in the high-risk villages had a 5-fold increased mesothelioma mortality compared to their lower exposed counterparts. There were no cases of mesothelioma in the comparison groups where no crocidolite was known to exist in the environment. In the third cohort study, one out of five cancer deaths (22%) was from mesothelioma. In contrast to the rarity of mesothelioma cases usually encountered in most studies, the three studies had the number of mesothelioma deaths not much fewer than that of lung cancer deaths, with a ratio between lung cancer and mesothelioma of the order of 1.3, 3.0, and 1.2, respectively.

Conclusions—The observation of numerous mesothelioma cases at Da-yao was a unique finding due mainly to their life time exposure to crocidolite asbestos, a naturally occurring substance on the ground surface soil. In addition, the finding of cases dying at a younger age or the relatively high ratio of mesothelioma cases to lung cancer could also be another unique result of lifetime environmental exposure to crocidolite asbestos. Although the commercial use of crocidolite has been officially banned since 1984, the incidence of mesothelioma has continued to show a steady increase, particularly among the peasants. Our observation made us speculate that the daily inhalation of asbestos fibers from dusty farm roads not only continued, but was also aggravated by the increasing number of speeding motor vehicles that left a cloud of dust behind them for the school children and walking peasants to breathe. In addition, the asbestos fibers from peeling walls and disintegrating asbestos stoves both could send asbestos fibers into the air when it was windy. Reduction of these exposures was proposed. Further, the establishment of a mesothelioma panel to verify cases, an exposure panel to reconstruct and assess previous personal exposure experience, and a cancer registry to accurately record all new cancer cases would greatly facilitate the future conduct of a longitudinal population study and provide accurate data for environmental risk assessment.

ASBESTOS-RELATED DISEASES FROM ENVIRONMENTAL EXPOSURE TO CROCIDOLITE IN DA-YAO, CHINA II. A CASE-CONTROL STUDY OF MESOTHELIOMA

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Objectives—Scattered patches of crocidolite, one form of asbestos, were found in the surface soil in a rural community of Da-yao, located in southwestern part of China. From an earlier clinical survey and cohort study, we reported an extraordinary number of mesothelioma cases. To ascertain the presence of dose response relationship between exposure intensity or duration and the development of mesothelioma, a case control study design was undertaken.

Methods—Thirty-four cases of mesothelioma were identified from the hospital records, of which 23 could be interviewed in the follow up effort. By matching these cases for age, sex and residence, 30 controls were selected from the same hospital patients, by excluding those with cancer, respiratory diseases or unknown diagnosis. Estimates for various exposure intensities were made for environmental exposures in the different time periods based on the extent of excavation and stove making going on at the time. In the few instances where high exposure in stove-making settings occurred, actual measurements made in simulated environments were used. The cumulative exposure index was the product of the number of years in residence and exposure density at that time.

Results—Mesothelioma cases were significantly associated with higher cumulative exposure index. In addition, there seems to be a dose-response relationship between time-adjusted cumulative exposure intensity and the development of mesothelioma, after a latency of an average of 50 years. Smoking was not a significant risk factor, either based on pack-years or history alone, but cancer in the immediate family was for mesothelioma.

Conclusion—Environmental crocidolite exposure is associated with mesothelioma and a dose response relationship between the lifetime exposure and the development of mesothelioma was found.

ASBESTOS RELEASE DURING REMOVAL OF RESILIENT FLOOR COVERING MATERIALS BY RECOMMENDED WORK PRACTICES OF THE RESILIENT FLOOR COVERING INSTITUTE

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This study assesses the asbestos levels observed during removal of resilient floor covering products using the "Recommended Work Practices" (1995) of the Resilient Floor Covering Institute or more protective methods (controls). Removals of sheet vinyl, 12" x 12" vinyl asbestos tile, 9" x 9" asphalt tiles and mastic were conducted. Bulk samples and air samples were analyzed by Polarized Light Microscopy, Phase Contrast Microscopy and Analytical Transmission Electron Microscopy-Yamate Level II protocol. Only a small number (0.7%) of fibers and structures counted by Transmission Electron Microscopy would be counted by Phase Contrast Microscopy as per the method specified by the Occupational Safety and Health Administration regulations. This poses a serious problem because all of the fibers and greater than 90% of the fiber bundles were respirable. These data illustrate the exposure potential during the removal methods tested and supports the necessity of controlling asbestos emission from such sources in order to protect human health and the environment.

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USE OF SIZE-SELECTED FIBERS TO EVALUATE THE CONTRIBUTION OF LENGTH VS CHEMISTRY IN FIBER CYTOTOXICITY.

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Studies have shown that asbestos can lead to lung disease. Therefore, substitutes have been developed that differ chemically from asbestos. However, fiber length as well as chemical composition may be an important factor in pathogenicity. The objective of this study was to investigate the role of length versus chemistry by monitoring the cellular effects of in vitro exposure to different length glass fibers (7 and 17•m) or three types of fibers (glass, chrysotile, or ceramic) of the same length. A dielectrophoretic classifier was used to separate fibers into specified length categories. Primary rat alveolar macrophages obtained by bronchoalveolar lavage were exposed to various concentrations of fibers. Cytotoxicity and inflammatory potency were assessed by lactate dehydrogenase and tumor necrosis factor α (TNF-α) release, respectively. Data show that 7•m glass fibers (100 μg/ml) caused 6% cell death while 17•m glass fiber caused 31% cell death (Blake et. al., 1998). We found that long glass fibers (at a cell:fiber ratio of 1:5) were twice as potent as short glass fibers in stimulating TNF-• production. Data indicate that MAP kinases, p38 and ERK, play a role in this TNF-α production. Long glass fibers were twice as potent as short glass fibers in activating p38 and ERK. Therefore, glass fiber length is an important factor in cytotoxicity and alveolar macrophage activation. To investigate the contribution of fiber chemistry to cytotoxicity, alveolar macrophages were exposed to chrysotile, glass, and ceramic fibers of similar dielectrophoretic size cuts (17μm target). Chrysotile appeared to exhibit the greatest cytotoxicity, i.e. 100-μg/ml chrysotile, glass, and ceramic fibers caused 30, 19, and 7% cell death, respectively. In conclusion, our results suggest that both length and chemistry play a role in cytotoxicity to alveolar macrophages. In contrast to in vivo exposures, our in vitro system failed to demonstrate the high cytotoxicity of ceramic fibers.

Directions to the Elihu Harris Building

Location:

1515 Clay Street
Oakland, California
(Corner of Clay Street and 16th Street)
12th Street BART Station

Buses Departing San Francisco Marriott:

Buses will depart the San Francisco Marriott promptly at 7:00am both mornings (May 24 and May 25) to transport passengers to the Elihu Harris Building. Following the Poster Session Reception on May 24th, buses will depart the Elihu Harris Building at 7:00pm for return to the San Francisco Marriott. On May 25th, buses will depart the Elihu Harris Building at 5:00pm for return to the San Francisco Marriott.

Directions from BART:

BART runs parallel to Broadway in downtown Oakland. The City Center (12th Street) Station is just two blocks east of the Elihu M. Harris Building in the City Center Retail Area. The SF/Concord, SF/Richmond and Richmond/Fremont lines stop at City Center Oakland. Riders on the Pleasanton/SF and Fremont/SF line must transfer to one of the above lines.

Once you arrive at the 12th Street BART Station, exit onto Broadway. Proceed North on Broadway toward 14th Street. Turn left onto 14th Street. (The Oakland Convention and Visitors Bureau will be on your left. The Frank Ogawa Plaza will be on your right.) Proceed one block on 14th Street to Clay Street. Turn right onto Clay Street. You will see the Harris State Building on the corner of Clay Street and 16th Street.

Driving Directions:

From Sacramento: Take Highway 80 South to the 580 Interchange; go East on 580 to the 980 Interchange; take the 980 to 880/Downtown Oakland Interchange; take the 18th - 14th Street exit (stay in the right hand lane) and go to 14th Street. Turn left onto 14th Street, crossing over the freeway; go straight on 14th Street for four blocks to Clay Street. Turn left onto Clay Street. The Elihu M. Harris (EMH) Building is immediately on the left.

From San Francisco: Cross the Bay Bridge; stay in the middle right hand lanes and take 580 East; from 580 take the 980 to 880/Downtown Oakland Interchange; take the 18th - 14th Street Exit and stay in the right hand lane; go 4 blocks to 14th Street. Turn left onto 14th Street, crossing over the freeway; go straight on 14th Street for approximately 4 blocks to Clay Street. Turn left onto Clay Street. The Elihu M. Harris (EMH) Building is immediately on the left.

From East 580: Take 580 West to 980 to 880/Downtown Oakland Interchange; take 980 to the 18th - 14th Street Exit and stay in the right hand lane; go 4 blocks to 14th Street. Turn left onto 14th crossing over the freeway; go straight on 14th Street for approximately 4 blocks to Clay Street. Turn left onto Clay Street. The Elihu M. Harris (EMH) Building is immediately on the left.

From South 880: Take 880 North to 980 to Downtown Oakland Interchange; Exit 14th - 17th Streets and stay in the right hand lane for 2 blocks. Turn right onto 14th Street; go straight on 14th Street to Clay Street. Turn left onto Clay Street. The Elihu M. Harris (EMH) Building is immediately to the left.

Parking:

Clay Street Garage: 1414 Clay Street
$1.50 per hour; $10.00 max per day; 6:30am - 10:00pm
*Across the street from the EMH Building.

Central Parking City Center West: 1250 Martin Luther King Jr. Way
$1.00 per half hour; $10.00 max per day (if in before 9:30am); 6:00am - 11:00pm
*4 blocks from the EMH Building.

City Parking Garage: 1911 Telegraph Avenue
$.75 per hour; $3.50 if in by 9:00am; $5.00 max per day; 6:30am - 9:00pm
*5 blocks from the EMH Building.

Lunch Options near the Elihu Harris Building

Note: There over 150 restaurants within a 1 mile radius of the Elihu Harris Building. We have listed 20 options which have been reviewed by the San Francisco Chronicle. The included map is intended to help you navigate.

Battambang
850 Broadway (near Ninth Street)

Southeast Asian: Simple dining room in which to take a culinary tour of Cambodian food like stuffed chicken wings and curries. Good service. -Robin Davis

Yorkshire Fish and Chips
248 Grand Avenue (near Harrison)

Seafood: If you want fish and potatoes, this is the place. Although the tables are clean and the fish is fresh, overall the place is grubby. Menu falls off once you leave the basic fish and chips. -K.S.

Carrara's
2735 Broadway (at 27th Street)

California/Contemporary: Some fabulous dishes like pork loin chops with a saffron-hazelnut crust, hanger steak and flan brought by polished servers. Located in a car dealership. - K.S.

Gold Medal Restaurant
381 Eighth Street (near Webster)

Chinese: Standout Chinese barbecue and good menu of $5 dishes including salt and pepper pork. Chinese greens and deep-fried flounder. - K.S.

Italian Colors
101 Broadway (Jack London Square)

Italian: A nice option in Jack London Square with top-drawer service and a nifty atmosphere. - K.S.

Jade Villa
800 Broadway (at Eighth Street)

Chinese: One hundred varieties of dim sum at theis bustling plain-Jane restaurant. Good dumplings, foil wrapped chicken, barbecue pork bun and shrimp-stuffed mushrooms. Helpful service. - Robin Davis

La Furia Chalaca
310 Broadway (between Third and Fourth Streets)

South and Central American & Caribbean: Family affair Peruvian restaurant. Good dishes include potato fritters, seafood, caramel-filled cookies. Service is sweet but lacks efficiency. - Robin Davis

Oaktown Café
499 Ninth Street (at Washington)

California/Contemporary: Fine rustic food such as whole roasted fish, risotto and pasta. Excellent value-minded wine list. - K.S.

Peony
388 Ninth Street, No. 288 (at Franklin)

Chinese: The Asian dishes can be inconsistent, but you'll find excellent Thai-style catfish, oxtail in red wine, roast suckling pig. - Michael Bauer

Phnom Penh House
251 Eighth Street (between Alice and Harrison)

Southeast Asian: A long-standing, reliable spot for reasonably priced Cambodian food. Easy-going atmosphere. -K.S.

Pho 84
416 13th Street (between Broadway and Franklin Streets)

Vietnamese: Pleasing interior and nice wait staff. Try the mussels and snapper in coconut milk and onions. - K.S.

Pho Hoa-Lao II
333 10th Street (between Webster and Harrison Streets)

Vietnamese: An outstanding rendition of Vietnam's national soup. Speedy service and low prices. -K.S.

Roscoe's Chicken and Waffles
336 Grand Avenue (at Perkins Street)

American: An unusual combination of chicken and waffles is more than a gimmick: it's good eating. - J.S.

Saigon
1526 San Pablo Avenue (near Clay Street)

Vietnamese: Terrific Vietnamese food including Vietnamese crepes and 7 courses of beef served in a casual setting. - K.S.

Lunch Options near the Elihu Harris Building

Note: There over 150 restaurants within a 1 mile radius of the Elihu Harris Building. We have listed 20 options which have been reviewed by the San Francisco Chronicle. The included map is intended to help you navigate.

Shan Dong
328 10th Street

Chinese: A charming dive with exceptionally nice waiters can be a terrific bargain if you pick the right dishes like dumplings and steamed buns. -K.S.

Soizic
300 Broadway (at Third Street)

California/Contemporary: Artsy dining room and subtle, delicate dishes make this restaurant a personal expression of the owners -Robin Davis

Sushi Zone
388 Ninth Street, Suite 268 (Second Floor)

Sushi: Awesome lobster sashimi. Also very good sushi and other sashimi. Service can run hot and cold. -K.S.

Toutatis
719 Washington Street (between 7th and 8th Streets)

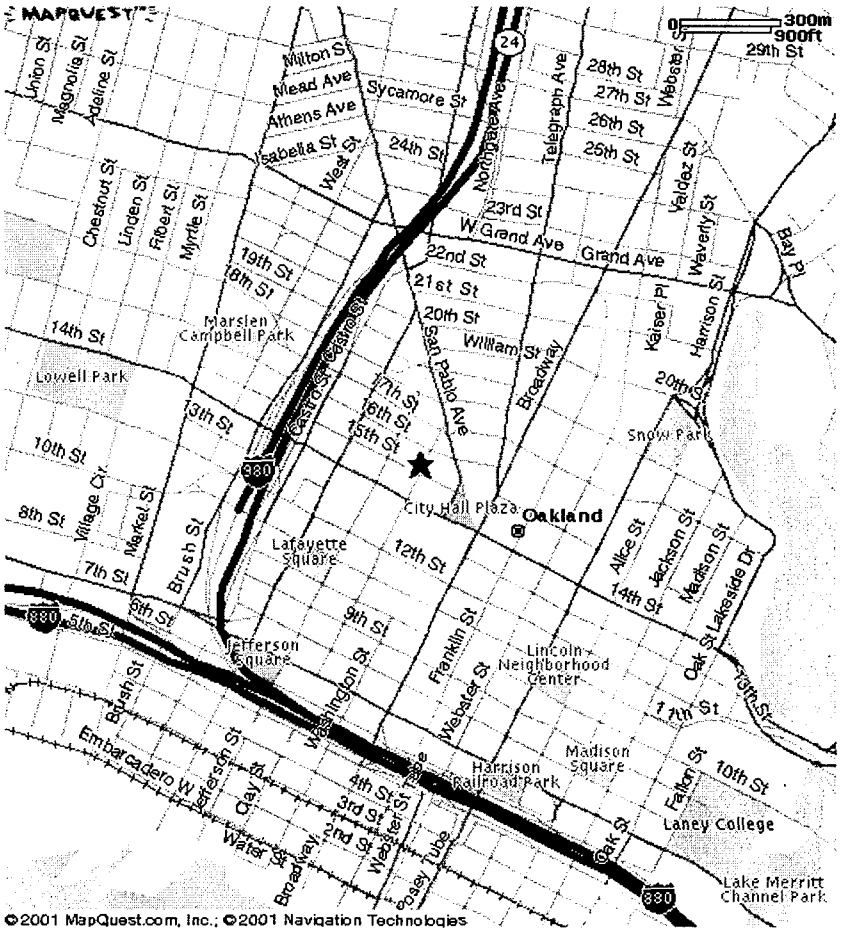
French: Crepes of all kinds highlight the menu at this welcome addition to old Oakland. The dessert crepes are particularly good. Cash only. - K.S.

Veronica's
1601 San Pablo Avenue (at 16th Street)

American: Terrific barbeque, decent home-style cooking and a friendly owner make this a great dining option for this section of downtown Oakland. -K.S.

Vi's
724 Wester Street (between 7th and 8th Streets)

Vietnamese: Vietnamese noodle soup is the name of the game here, though duck noodle soup outshines usual pho. - Robin Davis



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Asbestos Fact Sheet

EPA U.S. Environmental Protection Agency

Frequently Asked Questions Regarding Asbestos

Q. *What is asbestos?*

A. Asbestos is the name given to a number of naturally occurring minerals that have been mined for their useful properties. Asbestos is composed of silicon, oxygen, hydrogen and various metal cations (positively charged metal ions). Unlike most minerals, which turn to dust particles when crushed, asbestos breaks up into fine fibers that are too small to be seen by the human eye.

Asbestos appealed to manufacturers and builders for a variety of reasons. It is strong yet flexible, and it will not burn. It conducts electricity poorly, but insulates effectively. It also is resistant to corrosion. Asbestos may have been so widely used because few other available substances combine the same qualities.

Q. *What happens to asbestos when it enters the environment?*

A. Asbestos can enter the air and water from the weathering of natural deposits and the disintegration of manufactured asbestos products, such as insulation. Small fibers may remain suspended in the air for a long time before settling. Larger fibers tend to settle more quickly. Asbestos fibers are not able to move through soil and they are not broken down to other compounds in the environment. Therefore, they can remain in the environment for decades or longer.

Q. *How might humans be exposed to asbestos?*

A. Humans may be exposed to asbestos by breathing asbestos fiber in the air from a number of sources, including working in industries that mine, make, or use asbestos products or near a building containing asbestos products that is being torn down or renovated. They can also be exposed by drinking water that contains asbestos from natural sources or from asbestos-containing cement pipes in drinking water distribution systems.

Q. *How can asbestos affect human health?*
A. Asbestos mainly affects the lungs. Changes in the membrane surrounding the lung are quite common in workers exposed to asbestos. These are also sometimes found in people living in areas with high levels of asbestos in the air.

Breathing very high levels of asbestos may result in a slow buildup of scar-like tissue in the lungs and in the membrane that surrounds the lungs. This disease is called asbestosis, and is usually found in asbestos workers and not in the general public. Health studies that were conducted on people living near an asbestos-contaminated vermiculite mine in Libby, MT have found unusually high cases of asbestos in non-mine workers. People with asbestosis have shortness of breath, often along with a cough and sometimes heart enlargement. This is a serious disease and can eventually lead to disability or death.

Q. *How likely is asbestos to cause cancer?*
A. The Department of Health and Human Services (DHHS) and EPA have determined that asbestos is a carcinogen— it is known to cause cancer in people. There are two types of cancer caused by exposure to high levels of asbestos: cancer of the lung tissue itself and mesothelioma; a cancer of the membrane that surrounds the lung and other internal organs. Both of these are usually fatal. These diseases do not develop immediately after exposure, but may be discovered many years later.

Interactions between cigarette smoke and asbestos increase a person's chance of getting lung cancer. Studies of workers suggest that breathing asbestos can increase the chances of getting cancer in other parts of the body (stomach, intestines, esophagus, pancreas, kidneys), but this is not certain.

It is not known whether ingesting asbestos causes cancer. Some people who had been exposed to asbestos fibers in their drinking water had higher-than-average death rates from cancer of the esophagus, stomach, and intestines. However, it is not known whether this was caused by asbestos or by something else.

Q. *Is there a medical test to show whether humans have been exposed to asbestos?*
A. Chest X-rays cannot detect asbestos fibers, but can detect early signs of lung disease caused by asbestos. Other tests (lung and CAT scans), are also useful in detecting changes in the lungs.

Tests exist to measure asbestos fibers in urine, feces, mucus, or material rinsed out of the lung. However, low levels of asbestos fibers are found in these body fluids in nearly all people, so higher-than-average levels can only show that you have been exposed to asbestos, not whether you will experience any health effects.

Q. *Has the federal government made recommendations on how to protect humans from exposure to asbestos.*
A. Since 1989, EPA has banned six asbestos-containing product categories: corrugated paper, rollboard, commercial paper, speciality paper, flooring felt, and new uses of asbestos.

EPA does NOT track the manufacture, processing, or distribution in commerce of asbestos-containing

products. Therefore, consumers or other buyers should inquire as to the presence of asbestos in particular products.

EPA has established regulations that require school systems to inspect for damaged asbestos and to eliminate or reduce human exposure by removing the asbestos or by covering it up.

Also, EPA has set a limit of 7 million fibers per liter (MFL) as the concentration of long asbestos fibers that may be present in drinking water.

Q. *What products contain asbestos?*
A. Asbestos is found naturally throughout the world. It is mined in the United States, Canada, the former Soviet Union and South Africa. Asbestos is commonly used as for insulation and fire proofing. Many everyday products in use today contain asbestos, including:

- Thermal insulation
- Roofing paper
- Cement board and pipe
- Insulated sprayed coatings
- Thermal pipe wrap
- Trowelled coating
- Insulation board
- Corrugated paper
- Pipe wrap
- Absorbent packing
- Hydroponics brake pads and shoes
- Fire protection
- Sealants
- Paints
- Molten metal insulation
- Molded products
- Vermiculite

Q. *If people think they might have asbestos-containing insulation in their home, what do you suggest they do?*
A. If people think they have asbestos-containing insulation in their attic or walls, they should leave it alone. As long as the walls or attic insulation is in good condition the asbestos will not harm humans. If they are still concerned, it probably makes sense to have the material tested to see if it contains asbestos.

Q. *Can people test the material themselves?*
A. We suggest hiring a trained consultant or contractor to collect the sample and get it analyzed at a laboratory. We discourage disturbing any material potentially containing asbestos without proper training on appropriate safety precautions.

Q. *What should be done if the material is found to contain asbestos?*
A. Depending on the asbestos levels in the samples, where the material is located, and the condition of the material, you may want to consider getting the air in your home tested just to be sure the asbestos is not getting into the air.

Q. *If there is asbestos in the insulation, should it be removed?*
A. If the insulation is damaged and the potential exists that the asbestos fibers could become airborne, you might want to consider having it removed. Before taking that step, homeowners should consider a

number of factors. First, is the potential for exposure to the asbestos. Removing asbestos-containing materials must be performed by a certified professional and is typically very expensive. People should not attempt to remove the materials themselves. Second, if the insulation is not exposed to the home environment–for example, it is sealed behind wallboards and floorboards or is isolated in the attic that is vented outside or the insulation is in good condition, the best advice would be to leave it alone.

Asbestos Fact Sheet

EPA U.S. Environmental Protection Agency

Libby, Montana FAQs

Q. *Why has Libby, Montana, been in the news?*
A. From the 1920s to 1990, vermiculite, a material used in building insulation and as a soil conditioner, was mined in Libby, Montana. Unfortunately, the vermiculite from the Libby mine was contaminated with a form of naturally occurring asbestos called tremolite-actinolite. Exposure to asbestos can cause lung cancer and a cancer of the lung lining called mesothelioma. Libby-area residents, those who had worked in the Libby mine, and those who processed the vermiculite in other locations showed abnormal rates for cancer and other illnesses related to asbestos exposure.

Q. *How did EPA become involved*?
A. In response to local concern and news articles about asbestos-contaminated vermiculite affecting the health of local residents, the U.S. Environmental Protection Agency, Region 8 sent an Emergency Response Team to Libby, Montana, in late November 1999. EPA was concerned about area residents being exposed to airborne asbestos and breathing in the tiny fibers. The Team immediately began assessing the situation and collecting information.

Q. *What has been EPA's first priority at the site?*
A. EPA's first priority was to determine if there was a current risk to public health from asbestos-contaminated vermiculite in Libby and, if there was, to take the necessary actions to reduce or eliminate these risks.

Q. *What has happened at the site so far?*
A. In conjunction with other local, state and federal agencies, some of the actions taken at Libby include:

- Conducting a medical testing program for people who lived or worked in the Libby area during the time the mine was in operation;

- Conducting environmental sampling to develop a better understanding of patterns of exposure;

- Working with other involved agencies to recommend actions that can be taken to limit further exposure to asbestos and to mitigate or prevent adverse health effects; and

- Providing residents complete and current information on asbestos-related health risks. Work with area physicians and other medical professionals to help them obtain up-to-date information on the diagnosis and treatment of asbestos-related diseases.

Q. *What has EPA done specifically?*
A. EPA is the lead agency for environmental sampling in Libby. In December 1999 the EPA team collected nearly 700 samples (air, soil, dust, and insulation). These samples were collected from area homes, businesses, and public buildings in Libby. EPA also installed air monitors at four locations in Libby, including the mine site, and read measurements from January-October 2000.

In January 2000, EPA released some air sample results. The results from two of the former vermiculite processing areas showed asbestos fibers present. In addition, two of the 32 home samples showed asbestos fibers, but only one was associated with the Libby mine. At these four sites, EPA instituted action to eliminate the source of exposure, reducing or eliminating any current risks to human health.

In March 2000, EPA collected more soil, dust, and insulation samples from area residences. EPA also re-analyzed the indoor air samples from 32 homes and three businesses to determine if lower concentrations of asbestos fibers were present. Test results showed that two of those homes had fibers associated with the Libby mine. EPA instituted action to reduce or eliminate the source of exposure at those two homes. The results from the dust samples showed one home with fibers associated with the Libby site. The insulation samples showed that three of the homes had insulation with a fiber content of 1-2 percent. Soil samples showed that two of the homes had soil with fiber content of 1.5-2 percent.

Q. *What are the other agencies, besides EPA, that are involved in this response action?*
A. EPA is working closely with local, state, and other federal agencies, including: the City of Libby; Lincoln County Commissioners and the Department of Environmental Health; the Montana Department of Environmental Quality (DEQ); the Montana Department of Public Health and Human Services (DPHHS); and the federal Agency for Toxic Substances and Disease Registry (ATSDR).

Q. *What other concerns does EPA have about the Libby, Montana, site?*
A. EPA is concerned about the health issues seen in people with little or no association with the vermiculite mine in Libby. EPA, along with ATSDR, is working closely with local, state, and other federal agencies to understand how these people have come into contact with asbestos-contaminated material and what can be done to prevent future exposure—in Libby and elsewhere.

Q. *What are EPA's next steps at Libby?*
A. EPA began additional sampling in Libby the week of March 5, 2001. Like the first round, this sampling effort seeks to obtain information of the level of asbestos fibers that occur in the air inside people's homes. This is done using stationary air samples, which reflect the average asbestos level in the house. At this time, EPA will also collect personal air samples, reflecting what a person actually breathes. This next effort will take approximately three months to complete.

Asbestos Health Effects

A fact sheet by
Cal/EPA's Office of Environmental Health Hazard Assessment

Asbestos is the common name for a group of naturally occurring fibrous silicate minerals that can separate into thin but strong and durable fibers. Asbestos deposits are located in many parts of California and are commonly associated with serpentine.

Asbestos is classified as a known human carcinogen by state, federal, and international agencies. Asbestos was identified as a Toxic Air Contaminant in 1986 by the Air Resources Board.

The principal forms of asbestos include chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite. All but chrysotile are classified as amphiboles, which tend to have a thin, needle-like appearance. Chrysotile breaks into curly fibers.

Asbestos fibers can cause health problems if inhaled. When asbestos fibers become airborne, they can be inhaled deep into the lung. Many fibers deposited in the lung are retained there for long periods of time, others may be translocated to other parts of the body (e.g., the lining of the lung and abdomen), and others are completely cleared, albeit slowly. The fibers can cause chronic local inflammation and disrupt orderly cell division, both of which can facilitate the development of asbestosis and cancer. Thus, inhalation of asbestos fibers can initiate a chain of events resulting in cancer or other asbestos-related illness, which may not become apparent for years, even long after the exposure has ended.

Asbestos is classified as a known human carcinogen by state, federal, and international agencies.

Most of the information on health effects comes from studies of workers exposed regularly to high levels of asbestos. In occupational settings all forms of asbestos have been shown to cause asbestosis, lung cancer and mesothelioma. Asbestosis is a noncancerous lung disease involving diffuse fibrotic scarring of the lungs. Persons with asbestosis can experience progressive shortness of breath. Lung cancer is associated with asbestos exposures; cigarette smoking and asbestos exposure multiply the risk of lung cancer beyond that caused by exposure to either of these materials separately. Mesothelioma is an incurable cancer of the lining of the chest cavity and abdomen.

People have been exposed to asbestos by living with asbestos workers or living in the vicinity of asbestos mines and factories. People exposed to asbestos in such non-occupational settings have also had asbestos-related diseases including cancer. While most asbestos-associated cancers are related to the intensity and duration of exposure, reports in medical journals have linked some mesotheliomas to short exposure periods, on the order of months. Even in these cases, however, usually many years (20 years or more) elapse between the time of initial exposure to asbestos and the development of mesothelioma. In addition, there are reports of markedly elevated mesothelioma rates in populations living in

areas in Greece, Turkey and New Caledonia with substantial quantities of tremolite in soil, particularly among individuals who used tremolite asbestos to whitewash their homes, resulting in substantial exposure. These populations had ongoing low-level as well as episodic high-level exposures to tremolite.

There are some data that indicate amphibole forms of asbestos are more potent than chrysotile in inducing mesothelioma (but equipotent in inducing lung cancer). However, the data do not allow conclusive statements in this regard. Chrysotile and tremolite forms frequently occur together. Since many factors impact the potency of asbestos, the quantification of risk is inexact and at the present time all forms of asbestos are treated in risk assessment as equally potent carcinogens for both lung cancer and mesothelioma.

Asbestos was used in many household and building products in the past. In part because of this indiscriminate dispersal of asbestos in the human environment in past years, it is common to find hundreds of thousands to millions of fibers in human lungs. Generally those with heavy exposures have greater asbestos lung burdens. For example, lung tissue taken from patients with mesothelioma often contains over a million fibers per gram of tissue.

"Background" rates of mesothelioma for the general population in the United States with minimal exposure to asbestos are about 1 to 2 cases per 1 million people, though in communities in which there has been substantial occupational exposure such rates may be several-fold higher. Background rates for lung cancer are higher mostly due to smoking. Asbestosis is generally associated with occupational exposures but non-occupational exposures, particularly to household contacts of people working in the industry, have resulted in asbestosis.

For individuals living in areas of naturally occurring asbestos, there are many potential pathways for airborne exposure. Exposures to soil dust containing asbestos can occur under a variety of scenarios, including children playing in the dirt, dust raised from unpaved roads and driveways covered with crushed serpentine, uncontrolled quarry emissions, grading and construction associated with development of new housing, gardening and other human activities. For homes built on asbestos outcroppings, asbestos can be tracked into the home and can also enter as fibers suspended in outdoor air. Once such fibers are indoors, they can be resuspended by normal household activities, such as vacuuming (as many fibers will simply pass through vacuum cleaner bags).

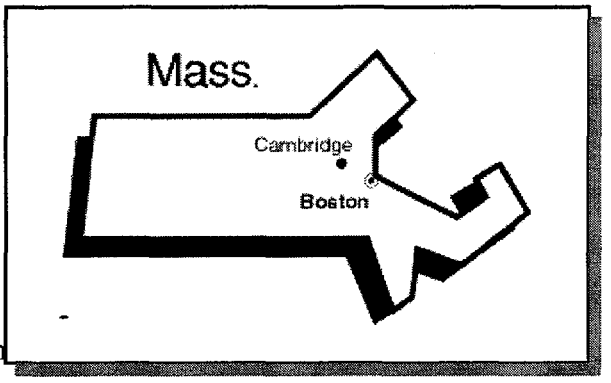
The general public exposed to low levels of asbestos may be at elevated risk (e.g., above background rates) of lung cancer and mesothelioma. The risk is proportional to the cumulative inhaled dose (number of fibers), and also increases with the time since first exposure. Although there are a number of factors that influence the disease-causing potency of any given asbestos, such as fiber length and width, fiber type, and fiber chemistry, all forms are carcinogens, and exposure should be minimized. The Air Resources Board has information on asbestos, including ways to reduce exposure, on its Web page at www.arb.ca.gov/toxics/asbestos.htm.

Asbestos Site Fact Sheet

EPA U.S. Environmental Protection Agency

W.R. Grace/Zonolite Site
Cambridge, Massachusetts

May 8, 2001



The Grace Zonolite site is located in an urban setting in downtown Cambridge, Mass., across the Charles River from Boston, and less than one mile from Harvard University.

Introduction

The W.R. Grace/Zonolite site covers 27 acres in a densely populated city neighborhood of downtown Cambridge, Mass. The site contains a wetland, a large pond, a large recreational facility maintained by the City of Cambridge, manufacturing buildings and paved parking areas. It is currently the headquarters of Grace Construction Products. Other densely populated areas nearby include the subway, recreational fields, and residential areas on three sides of the site.

The main contaminant of concern is asbestos. Asbestos contamination was suspected in surface soils in and around the site's paved public access, the entry to the Boston subway's Red Line Alewife station, one of the site's operating buildings, and the adjoining recreational facilities, which include football and baseball fields. EPA conducted sampling in Spring 2001 and determined there was no threat to human health and the environment at the site.

Site Background

Portions of the site have been in industrial or commercial use since the 1800s. Past activities on the site have included clay mining, brick production, chemical production, lumberyard and railroad operations, and ice cream production. The primary products of W.R. Grace and the company it merged with, Dewey and Almy Chemical Co., were rubber products, can-sealing compounds, gaskets, latex sealants and adhesives, silicone sealants, air-entraining agents for concrete, SodaSord, and sodium napthalene sulfonate (DAXAD). According to a report from W.R. Grace, asbestos may have been used in the development of brake-linings and for research on fireproofing materials. Production levels of these

chemicals are unknown. In the early 1980s, the Boston Metropolitan Bay Transportation Authority removed material from a chemical disposal lagoon and disposed of it in the Kingston, Mass., landfill, before constructing the subway's Red Line across the site.

There is no information about how many people have worked on the site in the past, but there are currently approximately 200 people working in the industrial office space near the site.

Site Investigation and Cleanup Activities

EPA performed a Preliminary Assessment in 1985, a Site Investigation in 1989. On April 3, 1990, EPA determined there was no threat to human health and the environment at the site and no further remedial action was planned. In Spring 2001, EPA reassessed the site, in cooperation with the Massachusetts "Superfund," or 21E program. The results of sampling showed there was no surface contamination and EPA concluded that no further action is required under the Federal Superfund program.

Communication and Outreach Activities

EPA issued a press release prior to sampling the site in early September 2000, and conducted a meeting with the Alewife Study Group, a local citizens' group, to update them on activities regarding the site. EPA's community involvement personnel were also at the site when sampling began. The results of the sampling were announced in another press release and public meeting in spring 2001.

Other Involved Parties

Stakeholders at the state level include MA DEP, which is actively involved through the 21E program. On the local level, the Cambridge Public Health Alliance has the responsibility for implementing the city asbestos ordinance. The Alewife Study Group, also is involved with site activities. The local and national news media have expressed repeated interest in the contaminated site.

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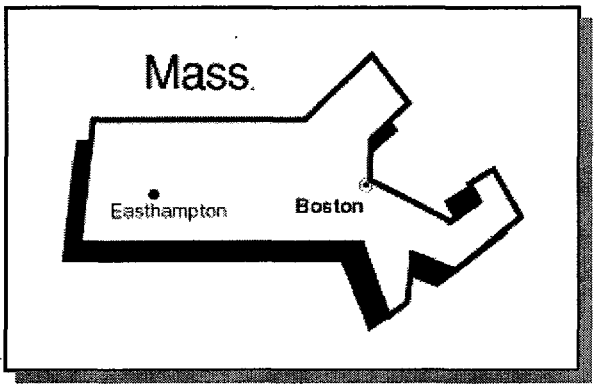
Asbestos Site Fact Sheet

EPA U.S. Environmental Protection Agency

W.R. Grace/Zonolite Site
Easthampton, Massachusetts

March 24, 2001



The Zonolite Company/Grace Easthampton site is located in a residential neighborhood in western Massachusetts, just west of I91, near the towns of Amherst and Northhampton.

Introduction

In May 2000, the Massachusetts Department of Environmental Protection (MA DEP) conducted an assessment of the W.R. Grace/Zonolite site located in Easthampton, Mass., and determined that vermiculite dumped on the site contained asbestos. For approximately 30 years, Grace Construction Products , a subsidiary of W.R. Grace and Co., manufactured Zonolite and Monokote which are commercial vermiculite insulation products. The vermiculite insulation contained tremolite asbestos which may pose a potential human health threat.

The U.S. Environmental Protection Agency (EPA) worked with the MA DEP to complete a sampling survey at the site. As a result of this investigation, MA DEP determined that the onsite waste dumping of vermiculite contaminated the onsite surface soil with asbestos. MA DEP will not be conducting the actual remediation activities at the W.R. Grace/Zonolite site, however, they will take the lead for ensuring that any necessary cleanup activities do occur.

Site Background

The 600-foot by 200-foot site was farmland until the early 1960s, when it was developed for commercial and industrial use. Half of the site is covered by a warehouse building, which used to be the Grace/Zonolite manufacturing facility, and pavement. The other half of the site is a wooded section of land that recently has been partially cleared. The manufacturing building is approximately 1,000 feet from residential houses.

From approximately 1963 through 1992, Grace Construction Products operated at the site under lease from its current owner, Oldon Limited Partnership, located in Agawam, Mass. During that time, local residents in nearby neighborhoods complained about dust generated by production. In the 1980s, Grace Construction Products responded to the community complaints by installing dampening measures to control the dust. Also during that time, most of the vermiculite waste was taken to a local landfill, which has since been capped. However, at least 1,000 cubic yards of vermiculite waste was dumped onsite. Before Grace Construction Products vacated the facility in 1992, the company cleaned the inside of the production building. Samples in early 2000 by an asbestos firm did not reveal the presence of asbestos in the building. JPS Elasomerics currently leases the property for material storage.

The W.R. Grace/Zonolite site and its cleanup are of particular interest to the state because Massachusetts has provided funding to construct a bike path on a former railroad right-of-way that parallels the property. Other sections of the bike path already have been built, but construction has been delayed along the section near the W.R. Grace/Zonolite site because of the potential human health threat. Construction will not resume on this section of the bike path until next year, when any necessary cleanup measures are completed and the site is deemed safe.

Site Investigation and Cleanup Activities

In May 2000, MA DEP, with assistance from EPA, completed an assessment of the W.R. Grace/Zonolite site and confirmed the presence of tremolite asbestos in the wooded area of the site as well as along part of the right-of-way. In early Fall 2000, MA DEP also tested the areas between the facility, up to the property line of the surrounding residential properties. The tests showed no evidence of asbestos contamination spreading from the facility to the boundary of the residential areas. As a result of the tests, no further testing has been done in the residential area.

In compliance with state law, W.R. Grace is investigating the site in order to develop a specific cleanup plan. This plan is expected to be implemented in Summer 2001. The state will not be involved in the decision on how to cleanup the site; however, the action taken must achieve a permanent solution, or result in tests showing "no significant risk." The state is operating under MA Chapter 21E of the General Law, MA Contingency Plan (MCP), 310.CMR.40. According to state personnel, there are no foreseeable enforcement actions at this time.

EPA's future involvement at the Easthampton site will depend on the cleanup plan developed by W.R. Grace.

Communications and Outreach

MA DEP conducted a public meeting in Easthampton on Dec. 12, 2000, to explain the results of its sampling. MA DEP regularly meets with the mayor of Easthampton and other local officials to inform them of recent activities associated with the site.

Other Involved Parties

At the local level, the citizens of Easthampton, MA are concerned about the overall welfare of their community and about delays in completion of the bike path following the old railroad track.

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Asbestos Site Fact Sheet

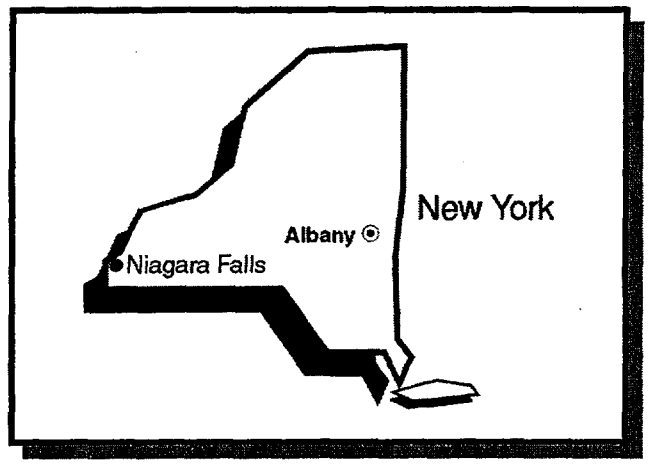
EPA U.S. Environmental Protection Agency

Carborundum-Unifrax Site
Niagara Falls, New York

March 26, 2001

Introduction

A 1953 U.S. Bureau of Mines (BOM) circular listed a domestic vermiculite exfoliation/expansion plant located in Niagara Falls, N.Y. and operated by Carborundum Corp. This site was added to the U.S. Environmental Protection Agency's (EPA) list of sites to investigate for potential asbestos contamination as a result of the vermiculite exfoliation process.



The Carborundum-Unifrax site is located in an industrial area of downtown Niagara Falls, N.Y.

EPA Region II has been unable to locate the exfoliation facility or any areas in Niagara Falls where asbestos-contaminated waste may have been disposed. It is a significant challenge to identify waste sites in this area because the plant has been out of operation for more than fifty years. The EPA On-Scene Coordinator (OSC), however, did locate two former Carborundum Corp. facilities in Niagara Falls. The first facility, Saint Gobain/Carborundum, is a ceramics facility. The second facility, Unifrax, uses vermiculite ore for production of a ceramic fiber paper. EPA investigated these two facilities and currently, is taking additional steps to obtain information on the location of the alleged exfoliation plant.

Site Background

Evidence gathered from the BOM circulars indicates that Carborundum Corp. operated a vermiculite exfoliation plant in Niagara Falls from the early 1950s until the early 1960s. Vermiculite expansion is the process of heating vermiculite ore, usually in a dry kiln at 2,000 degrees Fahrenheit, until the water trapped in the crystalline matrix of the vermiculite boils and expands the material by a factor of 10 to 15. This product is sold commercially.

EPA's discussions with senior Carborundum employees and a review of Sanborn maps of this area during this timeframe does not reveal additional information on the possible location of this facility. The Carborundum Corp. has been split up and sold to various companies over the last 25 years. Saint Gobain/Carborundum still maintains the ceramics division on Buffalo Avenue in Niagara Falls. Visual inspections of the area by the OSC revealed that many of the old Carborundum buildings at this location are being demolished or are vacant.

Around 1994, Unifrax purchased the fibers division of the Carborundum Corp. located on Whirlpool Street in Niagara Falls. Unifrax uses vermiculite ore for production of a ceramic fiber paper that is used in catalytic converters as a dampener and insulator around the honeycomb core material. The operation is conducted indoors and personal protective equipment is used when appropriate (*i.e.,* chamber loading). Unifrax also utilizes dust collection equipment in the chamber loading area. Unifrax indicated that they currently purchase the raw vermiculite ore from China, but in the past had purchased some vermiculite from W.R. Grace Co.'s mine in Enoree, S.C.

Site Investigation and Cleanup Activities

The EPA OSC conducted an initial inspection of the Carborundum location on Buffalo Ave. on June 13-14, 2000. The results of the investigation did not indicate that a vermiculite expansion plant had operated at this location.

In regard to the Unifrax operation, the EPA OSC interviewed the Unifrax vice president of technology. Unifax stated that the vermiculite process is confined within the building structure. Since there is no release to the environment (to ambient or outside air), the facility's operation does not appear to be covered under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). EPA will refer the site to OSHA for a follow-up inspection to assess whether site activities comply with OSHA's asbestos regulations.

EPA sent a CERCLA Section 104(e) information request to Carborundum Corp. officials to obtain information on vermiculite exfoliation operations in Niagara Falls in an attempt to locate the former facility and any areas where waste products may have been disposed. EPA will determine whether additional follow-up actions are needed after receiving the response to the information request.

Other Involved Parties

EPA is currently unaware of any actions being conducted by local, county or state officials.

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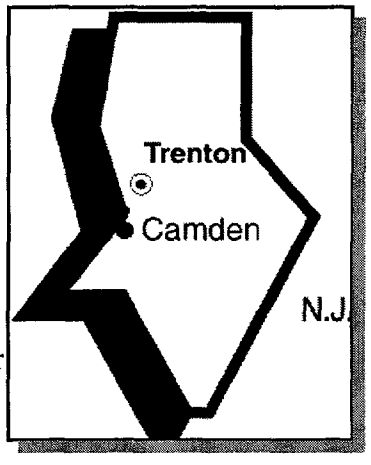
Asbestos Site Fact Sheet

EPA U.S. Environmental Protection Agency

Georgia-Pacific/Flintkote Corp.
Camden, New Jersey

December 18, 2000

Introduction



The Georgia Pacific/Flintkote site in Camden, New Jersey is located in an industrial area on the Delaware River.

The U.S. Environmental Protection Agency (EPA) identified the Georgia-Pacific/Flintkote Corp. property as a site with a potential for asbestos contamination after W.R. Grace Co. included the site on its list of "licensees" and "industry" partners, which was submitted in response to EPA's Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) section 104(e) information request. At the Georgia-Pacific/Flintkote site, Georgia-Pacific currently operates a sheetrock manufacturing facility that uses gypsum and vermiculite in its processes. The vermiculite used comes from a W.R. Grace mine.

EPA conducted an investigation of the site in June 2000, and concluded that no further Agency actions were necessary. EPA referred the U.S. Occupational Safety and Health Administration (OSHA) to the site to conduct a follow-up inspection to assess if the operation is in compliance with OSHA's asbestos regulations.

Site Background

The Georgia-Pacific/Flintkote site is located in an industrial area of Camden, N.J., bordering the Delaware River. In 1962, Flintkote constructed a plaster and wallboard manufacturing facility on the property. Flintkote sold the property to Genstar in 1982. Genstar continued to operate the same type of business. However, Domtar acquired the gypsum assets of Genstar in 1987. In April 1996, Georgia-Pacific Gypsum Co. bought the gypsum assets of Domtar and continues to produce gypsum wallboards on the site. An estimated 90 people are employed by Georgia- Pacific at this location.

Georgia-Pacific uses vermiculite–purchased from the W.R. Grace mine in Enoree, S.C.–to produce a product called "Fireguard C," which is a fireproof, half-inch sheetrock. The raw vermiculite ore, purchased in 50-pound bags, is placed in a mixer with gypsum plaster to form a slurry. The slurry mixture is the basis for the "Fireguard C" product. This product line is approximately two percent of the overall production at the plant.

Through an interview with the plant manager, EPA learned that all operations that utilize vermiculite are conducted indoors. When personnel are handling the bags of vermiculite, Georgia-Pacific instructs them to wear respiratory protection.

Site Investigation and Cleanup Activities

EPA conducted a site inspection of the facility on June 9, 2000, and concluded that since there is no release to the environment, no further CERCLA actions are necessary. EPA referred the site to OSHA for any follow-up investigation.

Other Involved Parties

EPA is unaware of any actions being conducted by local, county or state officials.

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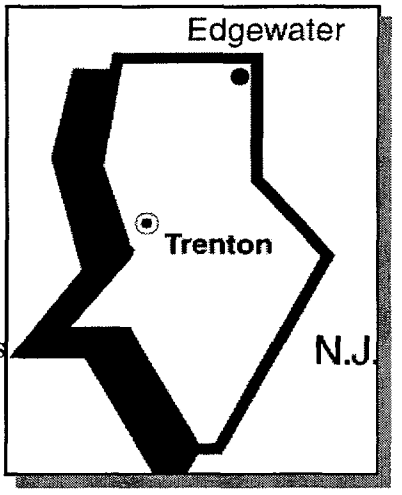
Asbestos Site Fact Sheet

EPA U.S. Environmental Protection Agency

Celotex Site
Edgewater, New Jersey

May 8, 2001

Introduction



The Celotex site in Edgewater, N.J. is located on the Hudson River in a heavy industrial area north-west of New York City.

The Celotex Corp. site in Edgewater, N.J. was identified by W.R. Grace Co. in its submitted list of "licensees" and "industry" partners in response to the U.S. Environmental Protection Agency's (EPA) Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) section 104(e) information request. EPA was concerned about the potential impacts on human health as a result of the presence of vermiculite in a landfill at the Celotex site. Based on this potential threat, EPA conducted a sampling investigation for asbestos. The New Jersey Department of Environmental Protection (NJDEP) also was concerned about the potential for asbestos contamination. They issued an administrative order on consent (AOC) to Edgewater Enterprises, LLC., the developers of the property, requiring the proper closure of the landfill.

Site Background

The Celotex site is located in a former heavily industrialized area of Bergen County adjacent to the Hudson River. This area currently is undergoing a major revitalization with the building of apartment and condominium complexes, shopping malls, and movie theaters along the river.

The Celotex property is bordered by the Hudson River to the east, River Road to the west, a residential area to the north and the Quanta Edgewater National Priorities List (NPL) site to the south. Celotex Corp. manufactured various building materials including sheet rock and ceiling tiles.

W.R. Grace shipped vermiculite ore to Celotex from its vermiculite mine in Libby, Mont., according to W.R. Grace records. Celotex disposed of gypsum debris and production waste, including the vermiculite, at the onsite landfill adjacent to the Hudson River.

Site Investigation and Cleanup Activities

On April 4, 2000, EPA conducted a site visit and sampling inspection at the former Celotex Industrial Park gypsum landfill to determine the presence of asbestos. The Agency collected twelve discrete grab samples (mostly surficial grab samples and a few at approximately one foot depth) of exposed gypsum material and surrounding soils. The samples collected at one foot depth were taken from holes previously dug by landscapers for the planting of trees. EPA also collected one sample from an erosion channel on the slope of the storm water retention basin. The samples were analyzed using Polarized Light Microscopy (PLM) method and Transmission Electron Microscopy (TEM) method.

EPA's Environmental Response Team issued a final report on June 2, 2000, indicating that six of twelve samples revealed asbestos fibers (as indicated by TEM) and one sample (as indicated by PLM) revealed 25 percent chrysotile, which is a type of asbestos fiber that is in used building materials. The sample which contained chrysotile was found on an old abandoned pier to the south of the gypsum landfill. This material appeared to be crumbled pieces of transite siding board that were severely deteriorating. EPA forwarded the final report to NJDEP.

Edgewater Enterprise is placing a two-foot clay cap over the contaminated gypsum landfill, where most of the contamination is non-hazardous solid waste, and the asbestos contamination is less than 1 percent. The cleanup should be completed by Fall 2001. The construction is done under the terms of an AOC issued under State cleanup regulations, including the New Jersey Statutory Authority (NJSA 13:1B-1) and the New Jersey Pollution Control Act, specifically the New Jersey Clean Water Act II (58:10A-1). NJDEP is overseeing the closure of the landfill and the installation of pavement or brick over the remainder of the site. In addition, under their permit for waterfront development, Edgewater Enterprise has constructed a storm water retention basin.

Other Involved Parties

Land developer Edgewater Enterprise, LLC. and their subsidiary, River Road will conduct all cleanup. EPA and NJDEP will continue to be involved with any further developments at the site. Concerned area residents also are likely to remain involved with the site cleanup.

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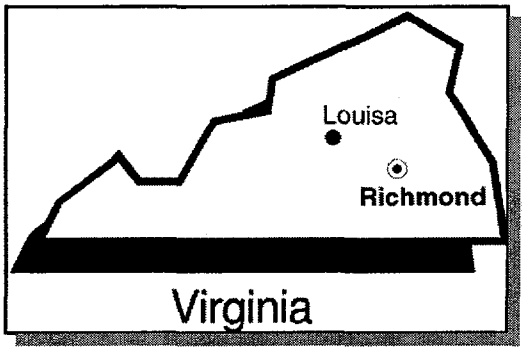
Asbestos Site Fact Sheet

EPA U.S. Environmental Protection Agency

Virginia Vermiculite Mine
Louisa, Virginia

March 26, 2001



The Virginia Vermiculite Mine in Louisa, Va., is located on State Road 22 in rural area of central Virginia.

Introduction

Virginia Vermiculite Mine, Ltd. owns and operates a mine in a rural residential area of central Virginia approximately 20 miles northeast of Charlottesville. The mine produces raw vermiculite for use in off-site manufacturing processes and was identified by EPA as a site to be investigated for potential asbestos contamination. The Mine Safety and Health Administration (MSHA) and the U.S. Environmental Protection Agency (EPA) have conducted asbestos sampling on the property and in the nearby community, respectively, to determine if there is a health threat posed by mine operations. As a result of this sampling, EPA has determined that there is no threat of off-site contamination and no further sampling or other action is warranted at this time. MSHA will continue to monitor the conditions at the mine.

Site Background

In the late 1970s, Virginia Vermiculite Mine, Ltd. purchased the15-acre to 20-acre property in Louisa, Va., from W.R. Grace Co. Virginia Vermiculite subsequently developed the mine during the 1980s. The company mines various grades of vermiculite and sells it for off-site processing.

The Virginia Vermiculite property consists of the former mine, processing facility; and a smaller active mining area. The two mine areas are separated by a wetland, and accessed from Virginia State Road 22. There are approximately six homes within one half mile of the site.

MSHA has been taking samples on the property annually or bi-annually for 20 years. Though EPA does not have documentation on how many people have worked at the mine historically, currently, Virginia Vermiculite employs 20 to 30 people at this site. There are known tremolite asbestos veins in the mine which are considered to be insufficient in concentration to be released off-site or pose a health threat. Mine operators have historically worked around these veins.

Site Investigation and Cleanup Activities

In August 2000, MSHA conducted bulk and air sampling at the Virginia Vermiculite site and subsequently released results showing asbestos in the ore and air onsite at levels above 0.1 fibers per cubic centimeter. The information was reported in the local news, suggesting the mining operations may pose a health risk to the local public and the workers onsite. Afterwards, MSHA called EPA and asked for support and cooperation in jointly investigating the site for potential asbestos contamination. MSHA's August sampling results were the first to show the possibility of asbestos contamination.

The EPA on-scene coordinator (OSC) assessed the site on Oct. 11-12, 2000 and again on Nov. 27-28, 2000. During the assessment, the OSC met with the Virginia Vermiculite plant manager and toured the property, including the processing facility and the surrounding area, to evaluate sampling locations for potential off-site migration of asbestos-contaminated particulates. The OSC also met with several local property owners, one of the mine's waste haulers, and the Louisa County Public Works director, who provided copies of analytical tests that were conducted by the County's consulting engineers and which indicated non-detection of asbestos in the material received at the landfill.

From Dec. 4-6, 2000, EPA took dust samples from residences in the immediate vicinity, and background samples from the public road and other areas in front of the mine. No asbestos was found in any of the samples. As a result, EPA has determined there is no threat to human health and the environment and no further action is required under the Comprehensive, Environmental Response, Compensation, and Liability Act.

However, MSHA plans to conduct additional testing at the site within the workplace. The OSC will continue to monitor MSHA's sampling efforts and assist them upon request.

Communication and Outreach Activities

Local news coverage has focused on the Green Spring National Historic Landmark District, which is an organization that opposes the mining operation, and on the various litigation efforts against Virginia Vermiculite over the continued operation of the mine.

Other Involved Parties

MSHA will continue to perform onsite sampling. The Green Spring National Historic Landmark District and other concerned citizens have been, and are likely to remain, involved in litigation with Virginia Vermiculite.

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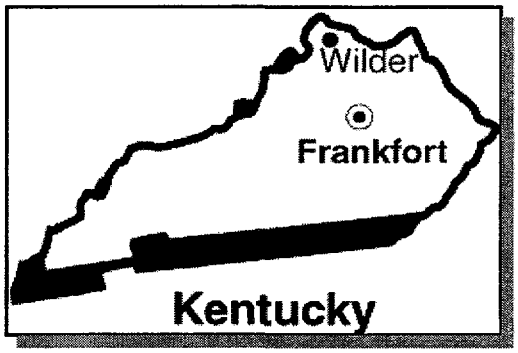
Asbestos Site Fact Sheet

EPA U.S. Environmental Protection Agency

Zonolite Co./W.R. Grace Site
Wilder, Kentucky

May 7, 2001



The W.R. Grace Wilder Plant is located in a flat, open field at the northern tip of Kentucky, just south of the Ohio border and the city of Cincinnati.

Introduction

The Zonolite Co./W.R. Grace Plant in Wilder, Ky., contains areas of heavy asbestos-contaminated residue as a result of vermiculite ore processing. The site is a flat, vacant lot with trees and shrubs along the perimeter and the south side of the site contains a steep edge with several areas of uncovered vermiculite. Asbestos is the only known contaminant. W.R. Grace is voluntarily conducting a cleanup of the site under the direction of the state of Kentucky.

Site Background

The Zonolite Co. began processing vermiculite ore in 1953. In 1960, W.R. Grace bought the property and continued processing vermiculite until the mid 1990s. During processing, the vermiculite ore was placed into a rotating kiln, where it expanded. The vermiculite product was removed from the kiln and used in fertilizers and as soil amendments, leaving behind asbestos-contaminated residue. This residue was loaded into dumpsters and disposed of behind several buildings on the property.

The present site owners, Harry Grau and Sons, refurbish petroleum product pumps at the site.

Site Investigation and Cleanup Activities

W.R. Grace has voluntarily agreed to construct an engineered-cap for the site to protect against airborne exposure to asbestos-containing material under Kentucky revised statute, KRS 224.01-400. In summer 2001, W.R. Grace will submit a management plan for the site to the state.

EPA investigated the site in July 2000. The Agency requested that W.R. Grace conduct more sampling to clearly define the outer limits of the asbestos contamination, and thus, to determine the size of the cap. Sampling should be completed in late Spring 2001, and the construction of the cap should begin in Summer 2001. EPA will monitor W.R. Grace's progress in constructing the cap.

Other Involved Parties

The involved parties include EPA, the Kentucky Natural Resources and Environmental Protection Cabinet, W.R. Grace, and the current property owners.

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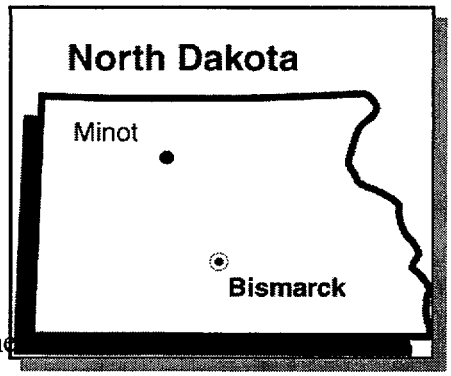
Asbestos Site Fact Sheet

EPA U.S. Environmental Protection Agency

Robinson Insulation Co. Site
Minot, North Dakota

April 17, 2001



The Robinson Insulation site is located on one to 2 acres of land in a commercial area of Minot, N.D., which is just south of the United States and Canadian border.

Introduction

Robinson Insulation Co. site, located in Minot, N.D., manufactured vermiculate insulation for almost 40 years. The facility consists of two buildings, which abut one another, located on approximately one to two acres of land. The site's immediate neighborhood includes other industrial and commercial facilities, and residential homes are within a few blocks of the facility. The U.S. Environmental Protection Agency (EPA) inspected the site and found tremolite asbestos. EPA considers this site a large scale cleanup project because of the amount of asbestos contamination.

Site Background

The Robinson Insulation Co. produced vermiculite insulation from the late 1940s through the 1970s, according to vermiculite shipment records from W.R. Grace's Libby, Mont. mine.
Former employees stated that the company piled vermiculite in the vicinity of the plant during the 1970s.

After Robinson Insulation stopped manufacturing insulations, the property was sold to a company that operated a retail insulation business. In 1986, Jessen Insulation Co. purchased the property. The company handled bagged vermiculite insulation and sold it to the local community. The City Parks Department, the property's current owner, purchased the site in 1993.

Site Investigation and Cleanup Activities

On Feb. 2, 2000, EPA, the Hazardous Waste Program Coordinator from the North Dakota Department of Health, and three representatives from the City Parks Department, visually inspected the site. There were no obvious piles of vermiculite insulation or ore. In addition, there was no indication of any former furnaces, stacks, hoppers, or silos.

EPA returned to the former Robinson Insulation site on Sept. 21, 2000, to conduct a closer inspection of the buildings and grounds. A close visual inspection of the grounds revealed vermiculite in numerous locations. Vermiculite also was seen in dust near inside one of the buildings. However, the building was closely packed with park equipment, thus EPA was not able to inspect the entire building to see if there was more vermiculite inside the building.

Six shallow soil/dust composite samples were collected from locations where vermiculite was seen. Sample analysis showed that all samples but one contained two percent tremolite asbestos. The analysis of the first sample showed trace levels (i.e., less than one percent) of tremolite asbestos.

EPA is considering a Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) order to cleanup the site because of the large scale of the project. EPA plans to begin remediation activities, such as excavation or capping, in late 2001.

Other Involved Parties

EPA is keeping local health department officials informed about the site and the cleanup process. In addition, the regional Agency for Toxic Substances and Disease Registry (ATSDR) is conducting a study on the past health effects in the adjacent neighborhood from the exposure to vermiculite.

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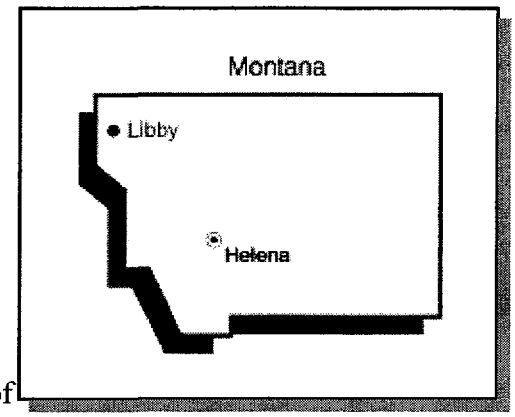
Asbestos Site Fact Sheet

EPA U.S. Environmental Protection Agency

W.R. Grace Vermiculite Mine
Libby, Montana

December 13, 2000



The W.R. Grace Vermiculite Mine in Libby, Mont., is located on State Road 2 in the northwest corner of the state.

Introduction

The W.R. Grace Vermiculite Mine in Libby, Mont. once produced approximately 80 percent of the world's supply of vermiculite. The historical extraction and processing of vermiculite ore released fibrous form amphibole asbestos into the environment, posing a threat to human health. Although the mine closed in 1990, a large number of current and historic cases of asbestos-related diseases have centered around Libby. When EPA sampled at and around Libby, a significant amount of asbestos-contaminated vermiculite (two percent to 10 percent asbestos by weight) was detected at two former vermiculite processing plants, the screening plant and the export plant. EPA conducted response activities at the screening plant and on a nearby road and is planning further actions in these areas and the surrounding neighborhood. In addition, EPA is directly overseeing removal actions and further sampling and analysis conducted by W.R. Grace. The site currently is used for non-asbestos related business.

Site Background

Vermiculite was first discovered outside of Libby in 1881 by gold miners. W.R. Grace purchased the mine in 1963 from Universal Zonolite Insulation Co. In addition to the mining operations, W.R. Grace also maintained an expansion operation onsite. Vermiculite expansion was the process of heating the ore, usually in a dry kiln at 2,000 degrees Fahrenheit, until the water trapped in the crystalline matrix of the vermiculite boiled and expanded the material by a factor of 10 to 15. W.R. Grace abandoned the expansion operation in 1981 and focused on mining for the next ten years.

In the mining operations, beneficiated ore was trucked to the 21-acre screening plant, which separated the milled ore into five size-ranges for use in various products. From there, the materials were bagged in the 11-acre export plant and then shipped across the country, mainly by rail, for either direct inclusion in products or for expansion/exfoliation prior to use in products.

At one time, there were approximately 2,000 people working at the mine and other places in Libby. Approximately 150 to 200 people worked at the screening plant and the export plant.

After W.R. Grace closed the Libby mine in 1990, the company sold the mine, the screening plant and the export plant to three separate entities. The mine was sold to Kootenai Development Co., which has done nothing with the mine. The screening plant is now a privately owned primary residence/nursery business called The Raintree Nursery. The export plant is currently owned by the city of Libby which leases it to Millwork West, a lumberyard and building materials supplier.
The screening plant and the export plant are located 300 yards to 400 yards from a residential area. At one time, adjacent to the export plant were two baseball fields that attracted many neighborhood children.

On Oct. 26, 2000, ATSDR released the preliminary results of health screening tests for asbestos related disease that were conducted on 6,415 people who lived or are living in the Libby area. The preliminary results showed 313 people with asbestos-related abnormalities (roughly five percent to six percent of those screened), including 125 people with heart related problems, 60 people who showed density in lungs, and 35 people who showed pleural thickening.

Site Investigation and Cleanup Activities

EPA is overseeing W.R. Grace's removal action in the export plant. Within the six buildings at the export plant, W.R. Grace is stripping out the insulation, vacuuming the fibers, and power washing the interior walls. They also are replacing any wooden flooring with gravel or concrete in the export plant. To remedy the external asbestos contamination of the 11 acres of land, W.R. Grace is excavating between 18 inches and 10 feet of soil, depending on the concentration of tremolite asbestos, and hauling it to the closed mine for disposal. Once the remedial activity is complete, W.R. Grace plans to cap the excavated area with clean soil from an adjacent uncontaminated area.

In the screening plant area, EPA demolished all existing structures–including one house, several greenhouses, and other structures–excavated soil, and stockpiled the debris on the property until a suitable long-term disposal site is identified. Although there will be no activity during the winter months of 2001, EPA anticipates returning to complete the excavation, dispose of the excavated material, and conduct final restoration work on the property in April 2001.

EPA plans to further evaluate of the results from the December 1999 to April 2000 sampling of 121 homes, six school buildings, and other potential asbestos source areas in Libby.

EPA will pave the contaminated Rainey Creek Road which was used during mining operations to connect the mine to the screening plant. EPA initially capped it with gravel after sampling in November 1999, indicated the presence of asbestos, but the agency will pave the road as a permanent solution.

Communication and Outreach Activities

EPA is providing information on response activities regularly to the Libby Community Advisory Group, the people of Libby, and city council members. EPA staff participate in a joint EPA/community meeting every two weeks, and on a weekly basis, answer questions on the Libby situation in the local newspaper. In September 2000, EPA hosted a four-day public meeting/conference, where toxicologists, doctors, and federal and state officials discussed asbestos issues; 200 local people attended.

Other Involved Parties

Also involved at the Libby site are the Montana Department of Environmental Quality, Montana Department of Public Health and Human Services, St. John's Lutheran Hospital, the city of Libby, the Libby Community Advisory Group, and the Lincoln County Health Department. Local newspapers have been covering the story for some time.

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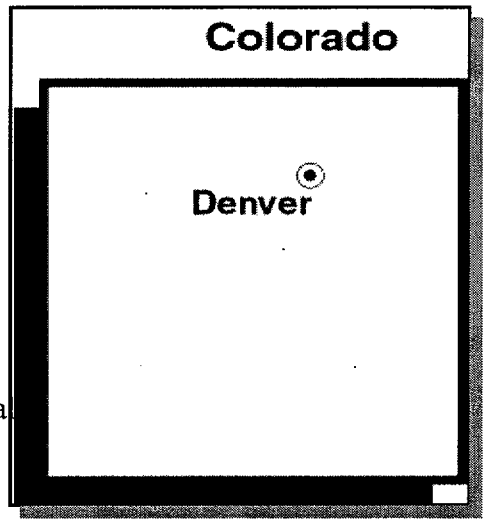
Asbestos Site Fact Sheet

EPA U.S. Environmental Protection Agency

Western Mineral Processing/ W.R. Grace Site
Denver, Colorado

April 17, 2001



The Western Mineral Processing/W.R. Grace Site is located in an industrial area in Denver, which situated in the middle of the state of Colorado.

Introduction

The Western Mineral Processing/W.R. Grace Site is located in an industrial area in Denver with residential and commercia property a few blocks away. Samples taken by the U.S. Environmental Protection Agency (EPA) confirmed the presence of tremolite asbestos at the site. EPA plans to conduct a removal action in late 2001 under the Comprehensive Environmental Response, Compensation, and Liability Act.

Site Background

Records obtained from W.R. Grace show shipments of vermiculite to Western Minerals Products/W.R. Grace from 1967 to 1988. However, these records may not be complete and the period of operation may be longer than the records indicate.

The facility property is paved with asphalt except for a strip of land located outside the facility fence on the south side. The site consists of a large processing building and a smaller office building. In addition, a rail line spur is located adjacent to the processing building, and there are three large silos.

Based on the presence of a glass debris landfill underneath the property, the property might have been used for a glass plant prior to the vermiculite operation which began operations in 1967. In 1990, Liquid Sugars Inc. (LSI), purchased the property from Western Minerals Products/W.R. Grace. Subsequently, in 1996, the property was purchased by Minnesota Corn Processors (MCP), a corn syrup company, that is the current site owner.

The buildings at the corn syrup company are the same buildings that were used by the vermiculite facility. The only changes MCP has made to the site was to add a storage tank.

When MCP acquired the processing building in 1990 after it was vacated by Western Minerals Products/W.R. Grace, there were no piles of debris or dust on the property. The silos also were free of debris. Prior to moving in, MCP did remove some asbestos insulation that had been installed in the office building.

Site Investigation and Cleanup Activities

EPA evaluated the facility on Aug. 21, 2000. Vermiculite was identified on the unpaved strip of land outside the facility fence on the south side. EPA took three shallow soil/dust composite samples on the unpaved strip of land. The analysis showed that the samples ranged from one percent to 12 percent tremolite/actinolite asbestos.

EPA intends to perform a Fund-lead removal action, such as excavation or capping, at the site. Cleanup will begin in the winter of 2001.

Other Involved Parties

EPA is keeping local health departments informed about the site and the cleanup process. In addition, the regional Agency for Toxic Substances and Disease Registry (ATSDR) is conducting a study on the past health effects in the neighborhood from the exposure to vermiculite.

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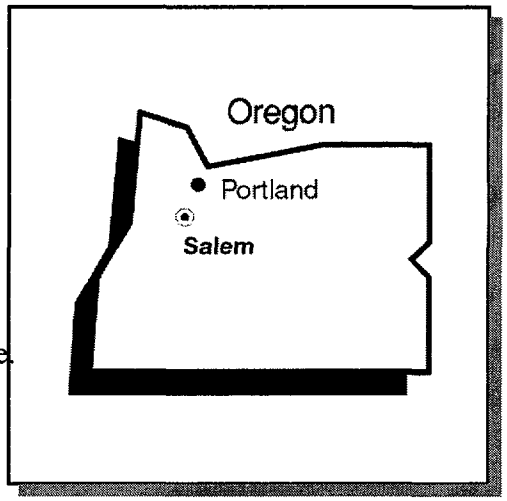
Asbestos Site Fact Sheet

EPA U.S. Environmental Protection Agency

Vermiculite-Northwest Site
Portland, Oregon

May 7, 2001



The Vermiculite-Northwest site is located in an industrial area north of Portland, Ore., just south of the Washington state border, where the Willamette and Columbia Rivers converge.

Introduction

The Vermiculite-Northwest site is situated in an industrial area just northeast of the Willamette River in Portland, Ore. The facility was used to manufacture, package, and store commercial vermiculite insulation products. Dust samples taken by U.S. Environmental Protection Agency (EPA) from interior ceilings confirm the presence of asbestos in the building. The current property owner is voluntarily removing the asbestos from the site, a certified asbestos abatement contractor to perform the cleanup work. The work began Jan. 4, 2001, and addressed 3,750 feet of rafters in the building's ceiling. The Oregon Department of Environmental Quality (DEQ) oversaw the cleanup work performed by the owner.

Site Background

Documents indicate that the facility began operating in the 1950s under the ownership of Vermiculite-Northwest, Inc., and produced Zonolite, a commercial vermiculite insulation. In addition, the company also manufactured acoustical plaster through a vermiculite expansion process. The vermiculite expansion process involves heating vermiculite ore until water trapped in the crystalline mixture boils and expands the material.

In the late 1960s, the business was taken over by W.R. Grace and Co., which continued to operate at the same address until 1996. Before vacating the property, W.R. Grace pressure-washed the building to remove any asbestos.

The current property owner is City Liquidators, Inc., which leases the building to Acme Scenic and Display, Inc. and Gronholm Manufacturing. Acme Scenic and Display constructs sets for movies, television, and the theater. The company plans to vacate the facility before the cleanup work begins. Gronholm Manufacturing fabricates pine dressers and other furniture.

Site Investigation and Cleanup Activities

EPA personnel visited the Vermiculite-Northwest site and conducted limited sampling. The samples were analyzed using transmission electron microscopy (TEM) and in two out of three samples asbestos was detected at just above the one percent threshold level. EPA also interviewed the property owner, current facility occupants, and a former Vermiculite-Northwest employee. As the lead agency pursuing follow-up activities at the Vermiculite-Northwest site, DEQ is dealing directly with the property owner, their contractor, and W.R. Grace, which is financing the cleanup work. DEQ is operating under the authority of Oregon Administrative Rule 340 Division 248, which governs asbestos removal, and is using the standard protocol for removal of 0.01 fibers/cubic centimeter for airborne asbestos. The state expects no enforcement action at the site.

EPA currently does not have plans for future involvement with the site other than maintaining regular communication with DEQ. However, the regional Agency for Toxic Substances and Disease Registry (ATSDR) staff have been in contact with EPA Region 10 Site Assessment Program officials regarding a "draft" Public Health Vermiculite Facilities Response Plan. EPA's possible future involvement with the "draft" plan is being discussed with ATSDR.

DEQ conducted a final asbestos abatement clearance inspection. Based on the inspection, DEQ has determined the building safe for occupancy. Clearance was granted April 3, 2001.

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Asbestos Site Fact Sheet

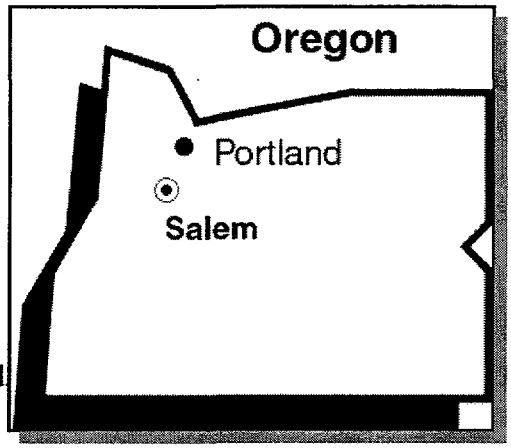
EPA U.S. Environmental Protection Agency

Supreme Perlite Site
Portland, Oregon

May 7, 2001

Introduction

The Supreme Perlite Co.'s facility, situated in a light industrial area in downtown Portland, Ore., manufactured, packaged and stored commercial vermiculite insulation. Historically, the facility received vermiculite from South African mines and from the W.R. Grace mine in Libby, Mont.



The Supreme Perlite site is located in a light industrial area of downtown Portland, Ore.

Soil samples collected by the U.S. Environmental Protection Agency (EPA) from areas along the exterior of the facility's manufacturing building revealed the presence of tremolite-actinolite asbestos. EPA is conducting a follow-up investigation in Spring 2001 to: observe current conditions; determine whether additional sampling is necessary to gauge the extent of asbestos contamination; and plan EPA's course of action, if necessary.

Site Background

Insulation manufacturing operations began at the Supreme Perlite site in 1960 under the ownership of Frank Petterson, who remains the owner. Vermiculite was used in manufacturing operations through the early 1970s. Currently the site is used to produce perlite, a volcanic glass product that does not contain asbestos. The Supreme Perlite site is approximately one city block, and contains one building that was used for vermiculite manufacturing. There is no documentation referring to vermiculite production levels or how many people worked at the site during the insulation manufacturing.

Site Investigation and Cleanup Activities

On April 26, 2000, EPA contractor personnel visited the site and conducted limited surface soil sampling where vermiculite was apparent on the ground and dust sampling inside the building near the former location of the vermiculite furnace and hopper. EPA analyzed the samples using transmission electron microscopy (TEM) and detected asbestos in four of five soil samples, ranging from trace levels to just above the one percent level. EPA is coordinating its follow-up investigation with the current property owner and provides regular updates on site activities to state and local authorities and the Agency for Toxic Substances and Disease Registry.

Personnel from the Oregon Department of Environmental Quality's (ODEQ) Asbestos Program accompanied EPA on their sampling visit and collected their own samples. These samples did not show any asbestos and ODEQ decided to take no further action.

The areas of contaminated soil identified by EPA during the screening assessment of the facility have been addressed by the current property owner. In April 2001, the property owner conducted a cleanup of the contaminated soil areas.

Other Involved Parties

Reporters from the Portland Oregonian were interested in the EPA and State sampling efforts.

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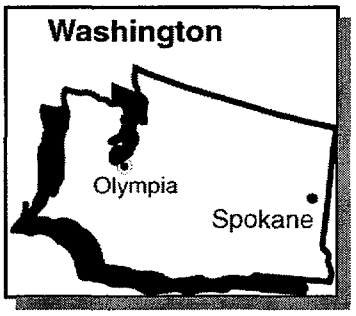
Asbestos Site Fact Sheet

EPA U.S. Environmental Protection Agency

Vermiculite -Northwest, Inc./ W.R. Grace Site
Spokane, Washington

May 7, 2001



The Vermiculite-Northwest, Inc./W.R. Grace site is located in a mixed light industrial and residential area in Spokane, Wash., in the southeastern corner of the state.

Introduction

The Vermiculite-Northwest, Inc./W.R. Grace site occupies one city block in a mixed industrial and residential area of Spokane, Wash. Vermiculite-Northwest Inc., manufactured, packaged and stored commercial vermiculite insulation. Soil samples collected by the U.S. Environmental Protection Agency (EPA) along the exterior of the manufacturing building revealed the presence of tremolite asbestos. EPA is planning to collect additional soil samples to determine the extent of the asbestos contamination in Summer 2001.

Site Background

Documents indicate that Vermiculite-Northwest, Inc. began producing Zonolite, a commercial vermiculite insulation that contains asbestos, in 1951. A former employee of Vermiculite-Northwest recalls that, at one time, there were 12 employees who worked at the facility, including hourly laborers and sales people.

W.R. Grace and Co. took over operations at this facility; however, the date of acquisition is not documented. A former Vermiculite-Northwest employee recalls that, during the mid-1960s, bags of finished Zonolite product listed W.R. Grace and Company as the manufacturer. Another former employee recounts that W.R. Grace closed the Spokane facility in 1973.

The current owner, Spokane County Engineers Office, purchased in the site in January 2000 and leases the building to Best Computers and Wilbert Vault Co. Best Computers uses a portion of the facility to store computer equipment. Wilbert Vault Co. uses another part of the property to store

concrete forms. A portion of the facility is subleased to a lighting supply company and to Les Scwab Tires.

Site Investigation and Cleanup Activities

On April 27, 2000, EPA contractor personnel visited the site, conducted soil sampling, and collected insulation samples from the facility's attic and its east wall. EPA analyzed the samples using transmission electron microscopy (TEM) and detected asbestos in seven soil samples collected from locations along the exterior of the building. Detections ranged from trace levels to just above the one percent level. The interior facility samples showed "non-detect." The EPA contractor also interviewed current facility occupants and a former Vermiculite-Northwest employee. EPA is coordinating its follow-up investigation with the current property owner, building occupants and nearby residents. EPA Region 10 provides regular updates on site activities to the state and local authorities and the Agency for Toxic Substances and Disease Registry.

Outreach Activities

Northwest Cable Network News interviewed the EPA on-scene coordinator (OSC) and featured the Vermiculite-Northwest, Inc./W.R. Grace site in one of its television broadcasts. Since the telecast, the OSC has received more than a dozen calls from people throughout the Pacific Northwest requesting general information on this and other potential asbestos sites.

Other Involved Parties

Washington State Department of Labor and Industries have indicated a willingness to help with outreach to the community.

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